# British Journal of
# UROLOGY

29

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P 25886

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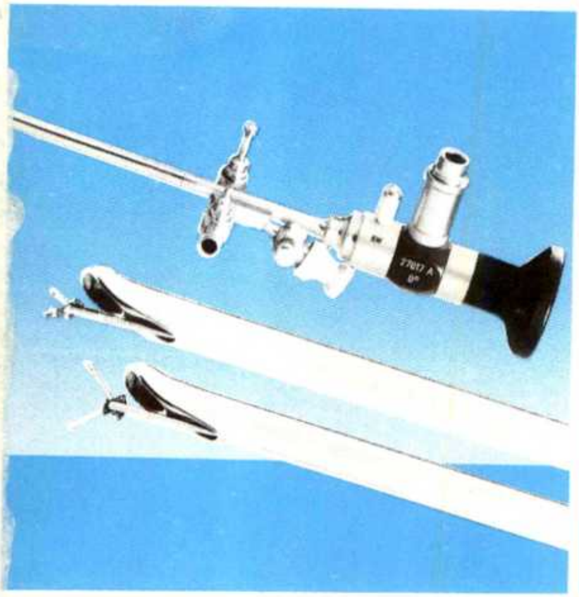

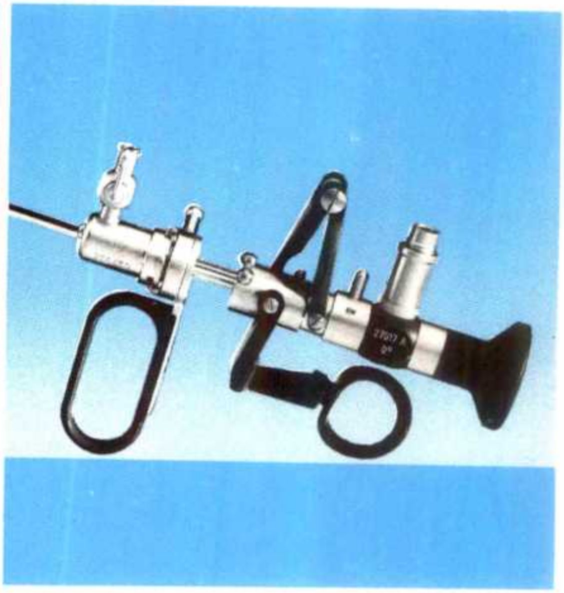

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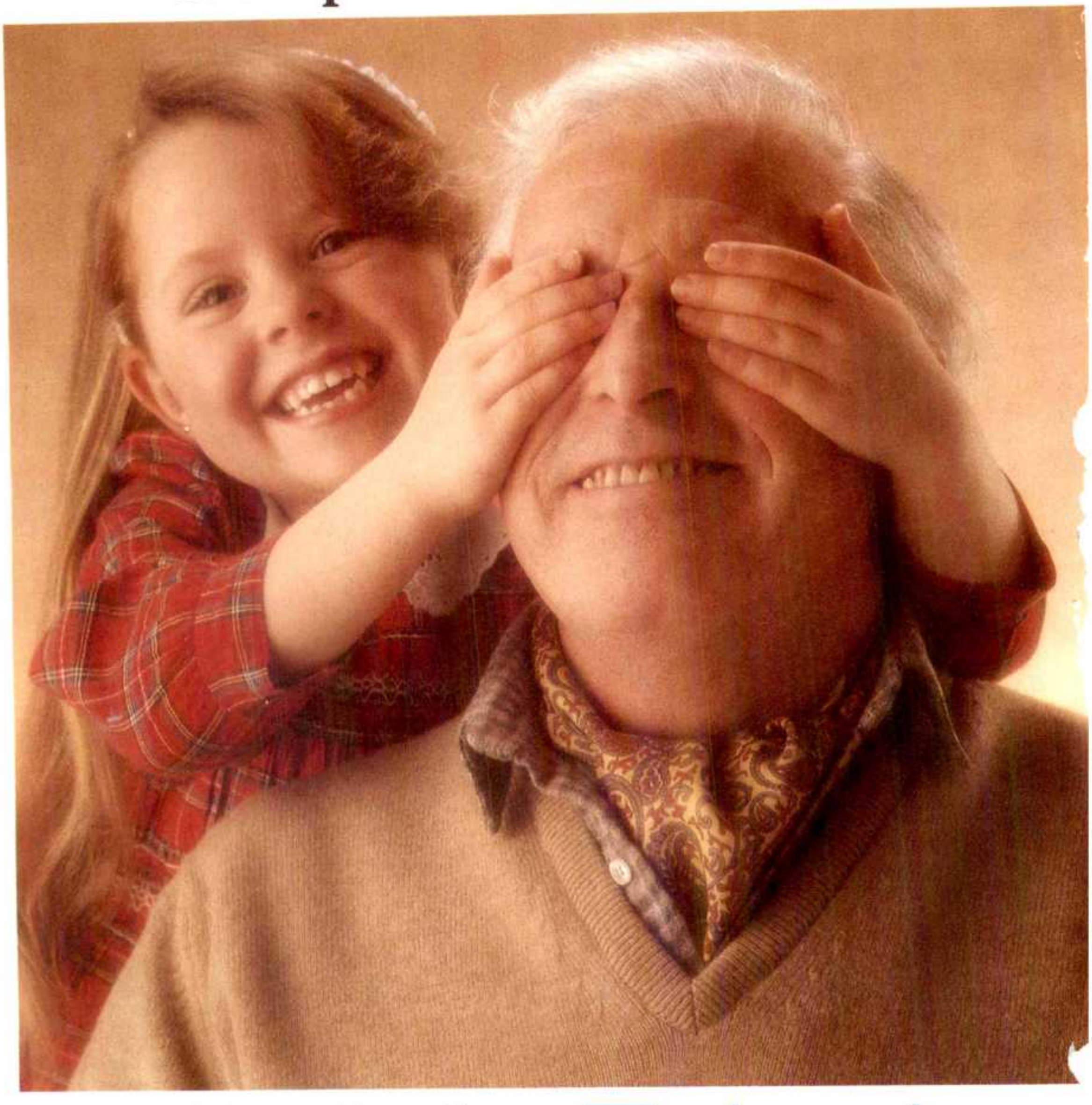

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**Reference** 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex'– a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.

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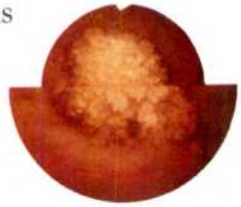

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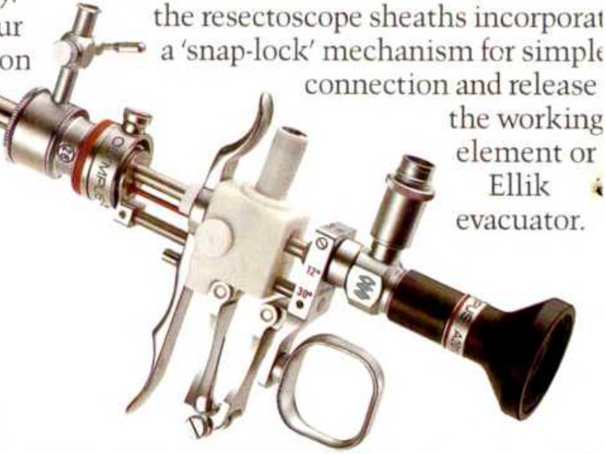

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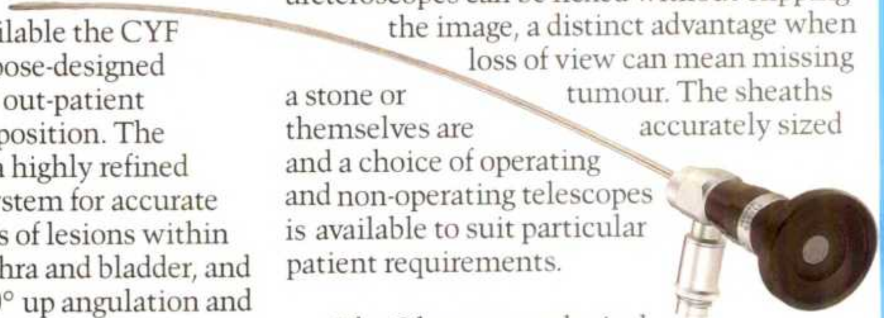

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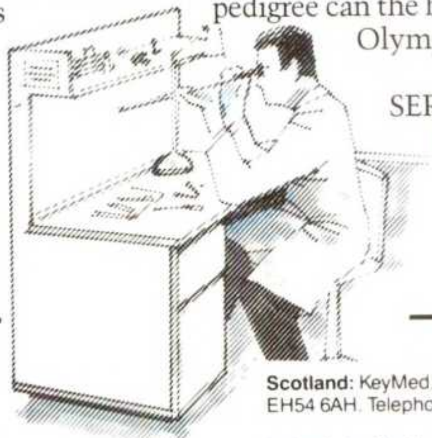

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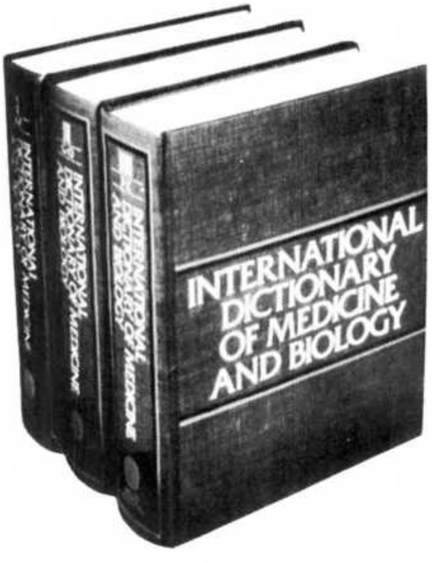

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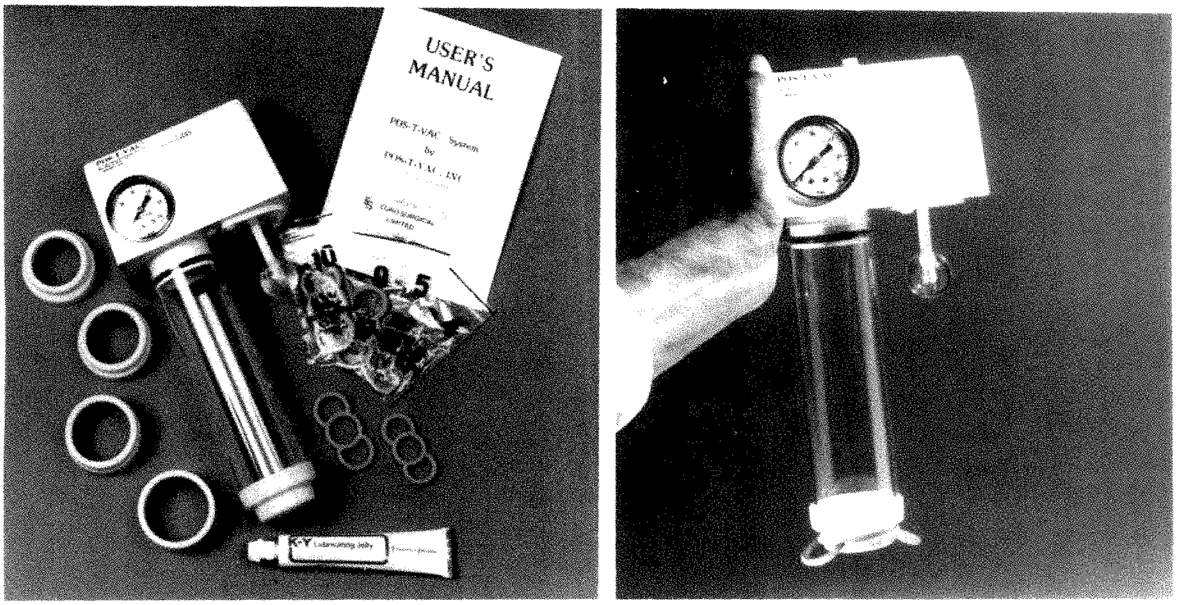

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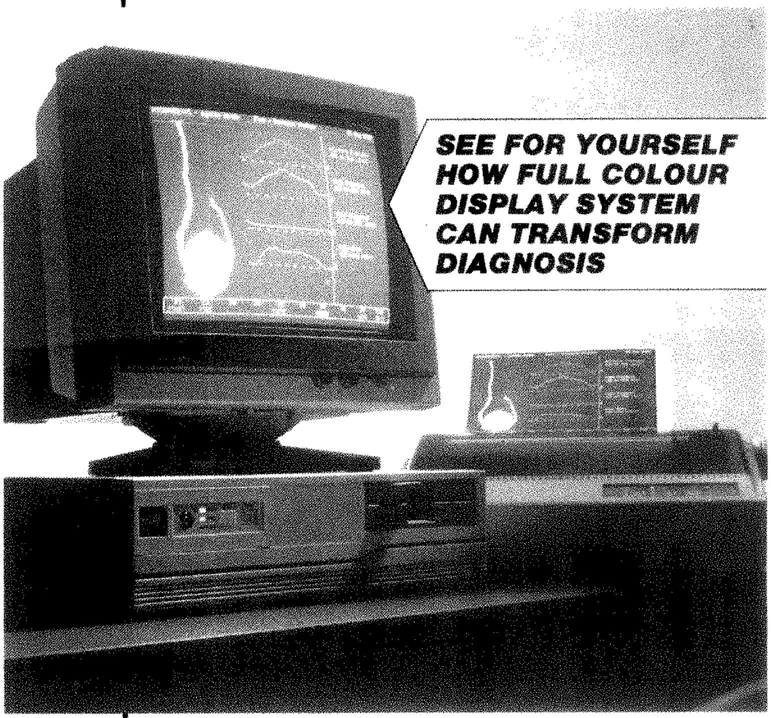

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REVIEW

# Molecular Biology of Urological Tumours

PAMELA J. RUSSELL, JOANNE L. BROWN, S. M. GRIMMOND and D. RAGHAVAN

*Urological Cancer Research Unit and Kanematsu Laboratories, Royal Prince Alfred Hospital; Department of Surgery, University of Sydney, Sydney, Australia*

In the past decade there has been a substantial increase in our understanding of the molecular basis of carcinogenesis and of the regulation of normal and malignant cell growth. As a result, a new terminology has arisen which reflects the rapid developments in this new field of molecular biology. In view of the rapidly evolving clinical relevance of these concepts, it is timely to review this field.

A number of genes termed proto-oncogenes (*c-onc*) have been reported to have a critical role in the regulation of normal cell growth and differentiation (Buckley, 1988). The products encoded by the proto-oncogenes cover a spectrum of cellular activities, including the production of growth factors and growth factor receptors, signal transducers (which carry a signal from the cell surface inside the cell) and nuclear transcription factors (proteins which regulate the expression of DNA) (Fig. 1). In malignant cells, certain proto-oncogenes can be activated (*c*-onc*) by a number of possible mechanisms (Fig. 2). The activated forms, now called oncogenes, have also been detected in tumour-inducing viruses (*v-onc*). Single oncogene activation can result in perturbation of mechanisms controlling cell growth and normal differentiation, leading to the onset of the neoplastic state. The multistep nature of neoplastic conversion, however, may involve the interaction of different types of activated oncogenes, *e.g.* those controlling nuclear events and signal transduction. Other factors, which may be critical to cell proliferation or differentiation, have not been linked to the role of known proto-oncogenes, perhaps reflecting insufficient study to date. These include growth factors which may be produced by the tumour cells which themselves carry the receptors for these growth factors, resulting in "autocrine" (or self) regulation of cell growth.

We review the changes in oncogene expression, growth factor production and chromosomal abnormalities that have been reported in this context in urological malignancies.

### *The role of oncogenes in experimental cancer*

Tumourigenesis is thought to involve a number of steps, one of which is "immortalisation", *i.e.* the ability of cells to divide indefinitely. Two techniques have been used to show that oncogenes have tumourigenic potential: transfection (*in vitro*) and construction of transgenic animals (*in vivo*). Transfection involves the transfer of genomic (total cellular) DNA isolated from tumour tissue or of DNA constructs (genetically engineered fragments of DNA) containing known *c*-onc* or *v-onc* under the control of various regulatory sequences (enhancers and promoters) into host cells. Traditionally, transfection has employed as recipient cells the immortalised fibroblast cell line NIH3T3. These

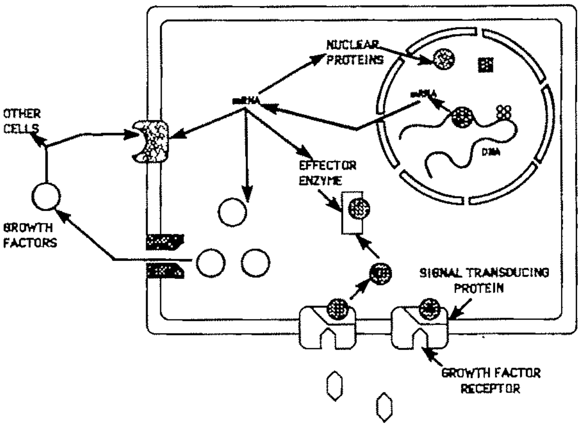

**Fig. 1** Products encoded by the proto-oncogenes.

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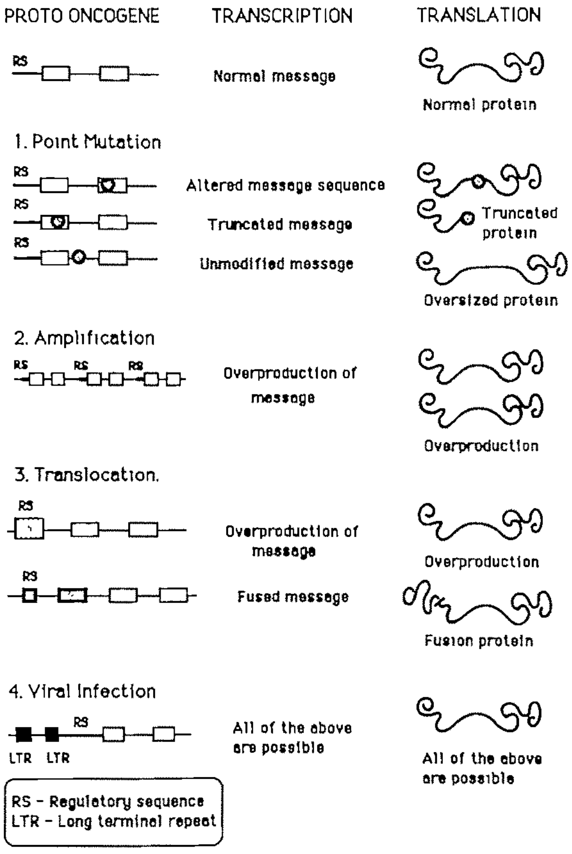

**Fig. 2** Activation of proto-oncogenes.

cells can be readily transformed by mutated *ras* genes (see section on Signal Transduction), whereas transformation of embryonic fibroblasts requires both an "immortalising" gene and an activated *ras* gene (Barbacid, 1987). It would be more relevant to transfect cells of the same tissue type as the cancer under investigation, and lines derived from normal tissues have recently been immortalised for this purpose, *e.g.* normal urothelial cells have been immortalised by transfection with the SV virus T antigen (Christian *et al.*, 1987).

The tumourigenic potential of presumptive oncogenes can be assessed directly *in vivo* by injecting DNA into one of the pronuclei of a recently fertilised egg and allowing the eggs to develop to term after placing them in pseudopregnant females, thus producing so-called transgenic animals. Breeding of these animals results in Mendelian inheritance of the gene of interest. The expression of the oncogenes can occur in several tissues or in a highly tissue-restricted manner, depending upon the attached regulatory sequences, and their biological effects on cellular proliferation and differentiation can be assessed (Compere *et al.*, 1988; Cory and Adams, 1988).

*Detection of activated oncogenes*

As described in Figure 2, oncogenes can be activated by point mutations (a change in a single base), amplification (multiple copies of the gene), translocation (rearrangement of chromosomes which result in a gene being placed under different regulatory sequences from normal), insertion of viral sequences which can alter the expression of the gene or increase the possibility of mutation, or by deletion of certain genes known as suppressor genes. The detection of such changes in tumours involves the use of various techniques, including transfection of genomic DNA from tumour material into recipient cells (as described above), but further analysis is required to determine the nature of the activation. The detection of oncogene mutations has generally been difficult and limited both in its sensitivity and in the types of mutations which can be detected. Three major techniques have been used: (i) RFLP analysis (Barbacid, 1987), (ii) oligonucleotide probing (Bos, 1988) and (iii) RNA mismatching (Lopez-Galindez *et al.*, 1988). More recently, the use of the polymerase chain reaction (PCR) (Saiki *et al.*, 1988) has overcome some of the limitations of these methods. The PCR can amplify small regions of a gene with known sequences using specific oligonucleotides as primers for enzymatic DNA extension. The advantages of this technique include a vast increase in both the sensitivity and the resolution of mutation detection as the sequence of a particular gene can be determined, and this provides the means to detect mutations in minute amounts of tissue.

The detection of amplification, translocation and viral insertions requires application of some of the above techniques together with additional analysis, including karyotyping, and *in situ* hybridisation. The effects of oncogene activation on expression of the gene can be detected by measuring levels of messenger RNA by Northern and dot blot techniques and/or by analysis of the levels of the protein product.

*Molecular changes in urological cancer*

The Table summarises the findings of amplified, deleted or mutated oncogenes and the production of growth factors, which have been described in various urological tumours to date. Different oncogenes have been altered, overexpressed or underexpressed in different cancers (as discussed below)

**Table** Alterations in Known Oncogenes or Growth Factors in Urological Malignancies

| *Alteration* | *Gene* | *Tumour studied* | *Reference* |
|---|---|---|---|
| Mutations | c-Ha-ras | Bladder TCCs | Malone *et al.* (1985) |
| | | Urothelial TCCs (codons 12,61) | Fujita *et al.* (1984, 1985) |
| | | *Bladder cancer cell lines* | |
| | | EJ (codon 12) | Tabin *et al.* (1982) |
| | | T24 (codon 12) | Reddy *et al.* (1982) |
| | | EJ and T24 (codon 12) | Taparowsky *et al.* (1982) |
| | | WEB | Marshall (1985) |
| | c-Ki-ras | Prostatic adenocarcinoma | Peehl *et al.* (1987) |
| | | *Bladder cancer cell lines* | |
| | | A1688 (codon 12) | Santos *et al.* (1983) |
| | | A1663 (codon 12) | Valenzuela and Groffen (1986) |
| | N-ras | HT1197 cell line (bladder) | Bos *et al.* (1986) |
| Amplifications | c-Ki-ras | Urothelial TCCs (1/38) | Fujita *et al.* (1984) |
| | c-myc | Prostatic adenocarcinoma | Fleming *et al.* (1986) |
| | c-erbB-2 | Renal adenocarcinoma | Yokota *et al.* (1986) |
| Translocations | c-myc | Hereditary renal carcinoma | Drabkin *et al.* (1985) |
| Deletion | c-Ha-ras | Bladder/kidney TCCs | Ishikawa *et al.* (1987) |
| | RB gene | Bladder cancer | Linzer 1988 |
| | c-Ha-ras | T24 bladder cancer cell line (last intron) | Cohen and Levinson (1988) |
| Chromosomal Deletions | 3p | Renal carcinomas | Kovacs *et al.* (1987) |
| | 9 | Bladder TCCs | Gibas *et al.* (1986) |
| | 11p | Bladder TCCs | Fearon *et al.* (1985) |
| | 10 | Prostatic adenocarcinomas | Atkin and Baker (1985a, b) |
| Over-expression | N-myc | Wilms' tumours | Nisen *et al.* (1986) |
| | c-Ha-ras | Prostatic adenocarcinoma | Fan (1988) |
| | Ha-ras | Prostatic adenocarcinoma | Viola *et al.* (1986) |
| | Ha-ras | Bladder TCCs | Viola *et al.* (1985) |
| | Ha-ras | Prostatic adenocarcinoma | Peehl *et al.* (1987) |
| | c-fms | Renal/prostatic carcinoma | Slamon *et al.* (1984) |
| | c-erbB-1 | Renal carcinoma | Real *et al.* (1986) |
| | c-erbB-1 | Bladder TCC | Neal *et al.* (1985)<br>Berger *et al.* (1987) |
| Growth factor production | G-CSF | Bladder cancer cell lines | Zinzar *et al.* (1985) |
| | TGF | Bladder cancer cell lines | Heckl *et al.*, unpublished |
| | Others | Bladder cancer cell lines | Guirguis *et al.* (1988)<br>Messing *et al.* (1984)<br>Brown *et al.* (1989) |

and so far no particular pattern of change appears to be associated with a given urological cancer type. This may reflect insufficient study to date or may relate to the complex, multistep nature of tumour development involving more than one oncogene. In general, studies have been limited to changes in a given oncogene in tumour specimens.

### *Growth Factors and Growth Factor Receptors*

A number of growth factors, growth factor receptors and related proteins are encoded by known proto-oncogenes (Schalken *et al.*, 1988). The activation of these proto-oncogenes will result in altered control of cellular functions. The following proto-oncogenes have been found to be activated in urological malignancies: *c-fms*, *c-erb*B-1 and -2.

The *c-fms* proto-oncogene encodes the receptor for colony stimulating factor-1 (CSF-1) which stimulates the growth and maturation of the macrophage cell lineage from haemopoietic stem cells. Expression of the *c-fms* gene was studied in a wide range of human tumours (Slamon *et al.*, 1984) and was found to be expressed in 4 of 9 renal carcinomas studied, with levels ranging from zero to very high in 1 of them, as well as in 3 of 4 poorly differentiated prostatic carcinoma cell lines (low levels) but not in corresponding normal tissue (Rijnders *et al.*, 1985).

The *c-erb*B-1 proto-oncogene encodes the epidermal growth factor (EGF) receptor, a protein which binds EGF and is localised to the plasma membrane. Like many of the other proto-oncogenes, the EGF receptor exhibits tyrosine kinase activity and is made up of an external ligand binding domain (the ligand being EGF) and an internal domain homologous to tyrosine kinases. These 2 regions are separated by a hydrophobic membrane domain (Westermark and Heldin, 1988). Using immunohistological techniques, the EGF receptor was demonstrated in both normal and malignant kidney tissues (Real *et al.*, 1986) but was expressed at levels 10- to 100-fold higher in renal carcinomas than in normal kidney. The EGF receptor is also present in low numbers in the cells of the basal layer of the urothelium (Gullick *et al.*, 1987). EGF was found to stimulate the growth of 4 cell lines derived from transitional cell carcinomas of the bladder, but only 1 of 4 derived from normal urothelium in a dose-dependent manner (Messing and Reznikoff, 1987). The expression of the EGF receptor may be a marker of certain stages of epithelial cell differentiation (Real *et al.*, 1986).

The c-*erb*B-1 proto-oncogene has been shown to be amplified in some squamous cell carcinomas and squamous carcinoma cell lines, none of which originated from urological malignancies (Yamomoto *et al.*, 1986). Thus amplification was not observed in any of the carcinoma cell lines derived from prostate, renal pelvis and bladder which were studied.

Studies of the EGF receptor by immunohistological methods in transitional cell carcinoma of the bladder (Neal *et al.*, 1985; Berger *et al.*, 1987) have demonstrated a strong correlation between the expression of the EGF receptor and an increase in the stage and grade of the tumours. Unfortunately, neither study looked at the histological subtype of the disease and so it is not known whether any squamous differentiation was present in those tumours that expressed the EGF receptor.

The proto-oncogene *c-erb*B-2 (also known as *HER-2*) encodes a glycoprotein (molecular weight 185,000 D) which is associated with the plasma membrane and has a high degree of homology with the EGF receptor gene *c-erb*B-1 (Yokota *et al.*, 1986). A ligand for this receptor-like protein has not been found and it does not bind EGF. The gene was first discovered as a transforming gene (termed *neu*) in rat neuroblastomas, in which it was activated by a point mutation in its transmembrane domain (Shih *et al.*, 1981). Like the EGF receptor gene, the *c-erb*B-2 gene has been found to be amplified in some human tumours. Up to 20-fold genomic amplification has been reported in 30% of primary breast tumours (Slamon *et al.*, 1987; Zhou *et al.*, 1987), where the presence of the amplification appears to correlate with the time of relapse and overall patient survival. The amplification of this gene appears to be associated with adenocarcinomas (Tal *et al.*, 1988) and has been described in human renal adenocarcinomas (Yokota *et al.*, 1986). In the urothelium the gene is expressed moderately in the basal layers (Gullick *et al.*, 1987). It has been suggested that the *c-erb*B genes may be important in the differentiation of epithelial cells, with the EGF receptor or *c-erb*B-1 gene being linked to squamous cell differentiation while the *c-erb*B-2 gene is linked to glandular differentiation (Yokota *et al.*, 1986). Similarly, altered expression of these genes may be involved in the differentiation and progression of squamous cell carcinomas and adenocarcinomas of various tissues.

In addition to the studies summarised above, it has been well documented that malignant urological cells have the ability to produce a variety of growth factors, whose relationship to known oncogenes has not yet been determined. Malignant cells grown *in vitro* have been shown to require fewer exogenously added growth factors than their normal counterparts (Sporn and Roberts, 1985), possibly due to their ability to produce and secrete growth factors, the receptors for which are expressed by the same cell or by other cells within the tumour cell population. This is reflected in a faster growth rate *in vitro* when tumour cells are seeded at high cell densities. Whilst decreasing the amounts of nutrients per cell, high cell numbers would increase the concentrations of mitogens derived from the cells themselves in the medium, thus allowing autonomous growth stimulation to occur (Messing *et al.*, 1984). Such autocrine mechanisms of growth stimulation enable the malignant cell populations within a tumour to become independent of the normal pathways of growth control.

Bladder cancer cells grown *in vitro* have been shown to produce and secrete factors which can stimulate the growth or other functions of either the same cells or of other bladder cancer cells. Three examples have been demonstrated to date. A factor distinct from the known growth factors, EGF and IGF-1 and -2, is produced *in vitro* by the human transitional cell carcinoma cell line 647V (Messing *et al.*, 1984) and increases the growth rate of these cells *in vitro*.

More recently, "autocrine motility factor" (AMF) has been found in the urine of patients with transitional cell carcinoma of the bladder (Guirguis *et al.*, 1988). AMF is also produced by the human TCC cell line T24P *in vitro* and induces the motility of these same cells in a chemotaxis assay. The motility of cancer cells may be very important in determining their ability to metastasise.

A further example has been found by the characterisation of a series of cloned cell lines derived from the human TCC cell line UCRU BL 17CL. This cell line secretes a factor which enhances the anchorage independent growth of 3 of the 9 clones. This autocrine stimulation of growth appears to be an intermediate step in the progression of these tumour cells (Brown *et al.*, 1989).

Other factors found to be secreted by urological cancer cells include granulocyte colony stimulating factor (G-CSF), which stimulates the growth of granulocytes from bone marrow of both normal and chronic myeloid leukaemia subjects, and transforming growth factors (TGF). G-CSF was shown to be constitutively expressed in the human bladder carcinoma cell line 5637 and was also produced by the bladder carcinoma cell lines T24 and J-82 and to a lesser extent by a primary culture derived from a papillary carcinoma of the bladder (Zinzar *et al.*, 1985). Primary cultures established from a bladder papilloma, normal prostatic epithelial cells and normal urothelium produced only low levels of G-CSF (Zinzar *et al.*, 1985).

TGF-$\alpha$ and -$\beta$ are functionally related to EGF. TGF-$\alpha$, which shares a high degree of homology with EGF and works through the EGF receptor, is thought to be the embryological equivalent of EGF (Westermark and Heldin, 1988). TGF-$\beta$ does not share sequence homology with EGF but can act synergistically with both EGF and TGF-$\alpha$ in inducing cell proliferation or differentiation (Westermark and Heldin, 1988). The human bladder carcinoma cell line KK-47 was shown to secrete TGF activities which were potentiated by the exogenous addition of EGF (Heckl *et al.*, unpublished).

In addition, in our laboratory, 3 bladder carcinoma cell lines, UCRU-BL-13CL, -17CL and -28CL, have been shown to produce the haemopoietic growth factor $\alpha$-thymosin (Russell and Oates, unpublished) and 1 of these, UCRU-BL-28, produces very high levels of insulin-like growth factor binding proteins (Russell *et al.*, unpublished). The relevance of these factors to cancer cell growth and their potential to protect the patient against myelosuppression from chemotherapy have yet to be determined.

### *Signal Transduction and the Ras Family*

The Ha-, Ki-, and N-*ras* genes are members of a multigene family which encode similar proteins collectively known as p21 (Barbacid, 1987). These genes can acquire transforming potential by single point mutations. The normal p21 proteins have been shown to have several biochemical properties, including the ability to bind GTP and to show GTPase activity. As a result of structural and functional homology between p21 and a well characterised class of signal transducers, the G proteins, it has been proposed that p21 acts as a signal transducing protein (Barbacid, 1987).

The role of G proteins is to carry messages from activated cell surface receptors to specific cytoplasmic effectors (often enzymes) that produce secondary messengers. Activated p21 proteins lack GTPase activity (McGrath *et al.*, 1984) because of a conformational change (an enlargement) in the catalytic site of the protein (Tong *et al.*, 1989). The loss of GTPase activity results in unrestricted production of secondary message. As it is likely that *ras* proteins transduce mitogenic stimuli, this can result in uncontrolled cell growth.

Experiments in which multiple copies of the *ras* gene are expressed have shown that its overexpression can lead to cellular transformation (Barbacid, 1987). An excess in signal transducing proteins can lead to overstimulation of the effector molecules in response to a normal extracellular signal. It has been proposed that phospholipase is the effector for *ras* proteins (Berridge, 1987). This enzyme produces secondary messages involved in the initiation of cell growth. The experimental finding that the artificial introduction of *v-ras* into a breast cancer cell line, MCF-7, frees the cells from oestrogen dependence (Kasid *et al.*, 1987) may be significant in the light of hormone independence of prostatic carcinomas after relapse from oestrogen therapy.

### *Ras and Urological Cancer*

To date, scant data exist on the frequency and type of *ras* mutations found in urological cancers. Mutated *ras* genes (including Ha-, Ki- and N-*ras*) have been detected at a frequency of less than 10% in primary bladder tumours (Bos, 1988). However, this estimate may be too conservative as it is primarily based on NIH3T3 transfection studies (Fujita *et al.*, 1984, 1985) (see section on the role of oncogenes in cancer). The present data on primary tumours can only be considered as preliminary and more work is required to determine the role of changes in the expression of the *ras* genes in urological malignancies.

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*Ras* mutations in bladder cancer cell lines grown in tissue culture have been more frequently described. The original studies of mutated Ha-*ras* were conducted using the human bladder cancer cell line T24 (Barbacid, 1987; Bos, 1988). The higher frequency of mutation found *in vitro* has been attributed to 2 factors; tumour progression and instability of the genome *in vitro*.

In addition to the point mutations which are generally confined to codons 12, 13 and 61 (triplets of bases whose sequence encodes a particular amino acid) and which alter the p21 *ras* product, recent work has demonstrated a point mutation in the promoter region (a regulatory region of DNA situated close to the coding sequence) of the *Ha-ras* gene of the T24 bladder carcinoma cell line (Cohen and Levinson, 1988). Similar mutations could have significant effects on *ras* gene expression in tumour specimens.

The Table shows that amplification of *ras* genes appears to occur infrequently in urological cancer. Amplification of Ki-*ras* was found in only 1 of 38 tumours by Fujita *et al.* (1985) and in a prostatic adenocarcinoma (Peehl and Stamey, 1986; Peehl *et al.*, 1987). A subline of the human bladder cancer cell line, MGH-U1, which possessed increased expression and amplification of Ha-*ras*, showed no differences in metastatic potential in nude mice when compared to the standard MGH-U1 cell line (Kovnat *et al.*, 1988).

Viola *et al.* (1985) reported that increased expression of the *ras* gene correlated with the grade and stage of human bladder tumours but this was not substantiated in other studies (Malone *et al.*, 1985). However, increased expression of *ras* correlated with higher grade prostatic tumours (Viola *et al.*, 1986) and with the potential of prostatic tumours to metastasise to the bone (Fan, 1988). In experimental studies Reznikoff *et al.* (1989) have shown that immortalised normal urothelial cells (see section on the role of oncogenes in cancer) transfected with the activated *ras* oncogene only become tumourigenic in nude mice when the p21 product is overexpressed; such clones also showed a loss of chromosomes 1p and 3p.

The Ha-*ras* locus is polymorphic and it has been suggested that several of its rare alleles may predispose to cancer. The frequency of rare Ha-*ras* alleles in individuals with a wide variety of cancers was observed to be 23% compared with 9% in unaffected controls (Krontiris *et al.*, 1985). However, recent studies (Ishikawa *et al.*, 1987) failed to detect any correlation between *ras* alleles in individuals with TCC of the bladder, ureter and renal pelvis or in normals.

The experimental observation that transfection of activated *ras* genes into NIH3T3 cells results in increased glycosylation of the cell surface (Bolsher *et al.*, 1988), and increased invasiveness by the cells, may be of significance in light of the finding that bladder tumour cells are heavily surface glycosylated compared with normal bladder (Debray *et al.*, 1986; Russell *et al.*, 1988).

Deletion of Ha-*ras* in urological tumours has been shown to be a relatively common event and may play a role in tumour progression; 38% of TCCs from heterozygous individuals were found to contain deletions of 1 allele (Ishikawa *et al.*, 1987). Chromosomal deletion of 11p (the region coding for Ha-*ras*) was also found in 5 of 11 bladder TCCs (Fearon *et al.*, 1985). The role of allelic deletion in tumour development is poorly understood but several consequences may result. Firstly, such events may unmask recessive mutations on the remaining Ha-*ras* allele. It is also possible that complex mechanisms (termed "transactivating") may increase expression of a single allele above normal levels (Ishikawa *et al.*, 1987). Deletion of 11p may result in the loss of more than just Ha-*ras*. Deletion of possible suppressor genes (as described later) or other cellular genes located on 11p may coincide with Ha-*ras* allelic loss. Finally, Ha-*ras* may be one of many loci that lose alleles during tumour development. This possibility is supported by studies on melanoma, where somatic allelic loss from a number of marker genes has been observed (Ishikawa *et al.*, 1987).

### *Cellular oncogenes encoding nuclear proteins*

Whether or not a gene is transcribed frequently involves interactions between specific proteins known as transcription factors, which bind to DNA to regulate gene transcription positively or negatively. This protein-DNA interaction is often associated with chromatin (Muller *et al.*, 1988). Interaction of cells with growth factors leads to rapid but transient transcription of certain proto-oncogenes (*e.g. c-myc, N-myc, L-myc, c-fos, c-myb, c-erb*A, *c-ski, c-ets, c-jun*) whose protein products are found in the nucleus. In some tumour cells the oncogene products survive longer than normal (Muller, 1986), possibly resulting in prolonged transcription of important cellular genes. There is mounting evidence to suggest that the protein products of these oncogenes are related to transcription factors. The best documented examples are (1) *c-erb*A, which encodes a thyroid hormone receptor regulating transcription of other genes in response to hormone binding (Sap *et al.*, 1986; Weinberger *et al.*, 1986), whereas the viral oncogene *v-erb*A is a constitutively activated transregulatory protein independent of ligand binding (Muller *et al.*, 1988) and (2) the protein derived from *v-jun*, which exhibits enhancer binding properties like AP-1, a human transcription factor important in regulating genes which govern cell growth (Bos, 1988), and which can be activated by phorbol ester tumour promoters.

Studies of these genes in urological malignancies have not been reported as yet. The *myc* genes have also been implicated in cell differentiation and in oncogenesis in various species in association with retrovirus insertion, gene amplification and chromosomal translocations. Expression of *c-myc* (or of the related *N-myc* or *L-myc* genes) is elevated in many tumour cells. Significantly higher levels of *c-myc* transcripts were observed in adenocarcinomas of the prostate than in benign hyperplasia samples (Fleming *et al.*, 1986). N- and c-*myc* are differentially expressed in normal developing human renal tissues and in Wilms' tumours. N-*myc* expression was markedly enhanced in 12 of 13 Wilms' tumours in the absence of gene amplification, and this was associated with down-regulation of c-*myc* expression (Nisen *et al.*, 1986). Amplification of the *myc* gene has been detected in *in vivo* selected (xenografted) cells of the PC3 prostatic adenocarcinoma cell line, compared with cells grown in tissue culture (Fukumoto *et al.*, 1988).

Aberrant chromosome structures, including homogeneously staining regions (HSRs) and double minute chromosomes (DMs) which are known to harbour amplified genes, are frequently noted in the karyotypes of human tumour cells. DMs containing amplified *myc* have been described in the HL-60 human promyelocytic leukaemic cell line as well as in the patient (*c-myc*, Dalla-Favera *et al.*, 1982), in small cell carcinomas of the lung (*c-myc*, Little *et al.*, 1983) and in neuroblastoma cell lines (*N-myc*, Kohl *et al.*, 1983; Schwab *et al.*, 1984). The *myc* amplification appears to correlate with more aggressive disease in these diseases (Seeger *et al.*, 1985), suggesting that it is associated with tumour progression rather than initiation.

Neither elevated nor constitutive *c-myc* expression alone is sufficient to produce tumours, as shown by studies of transgenic mice containing myc fusion genes (MMTV-LTR-*myc*, or Ig-*myc*) (Cory and Adams, 1988). Tumours of monoclonal origin develop only after a long latency period in a variety of tissues, including mammary gland (MMTV-LTR-*myc*) and B cells (Ig-*myc*), suggesting that additional co-operating functions, *e.g.*, as a result of "spontaneous" proto-oncogene activation, are required. Constitutive *c-myc* expression above a certain level may promote cell division and inhibit differentiation, thereby increasing the number of cells which are less mature but which have a greater proliferative capacity. This would allow accidental events which affect growth control mechanisms to create a malignant tumour of clonal origin. In support of this, experimental studies have shown that embryo fibroblasts cotransfected with both *myc* and the *ras* oncogene derived from the T24 human bladder carcinoma cell line become tumourigenic, whereas neither oncogene alone is tumourigenic (Barbacid, 1987).

### *Specific chromosomal abnormalities in urological cancer*

Extensive cytogenetic studies have revealed that a considerable number of human tumours are associated with consistent, specific chromosomal aberrations (Mitelman, 1983; Yunis, 1983). A striking concordance has been shown for the positions of proto-oncogenes and consistent chromosomal breakpoint regions (Rowley, 1983). For example, translocations which fuse the cellular proto-oncogene *myc* (chromosome 8 in man) to a different promoter (regulatory sequence) result in disruption of normal transcription of *myc* as in Burkitt's lymphoma (Klein, 1981; Shen-Ong *et al.*, 1982). Similarly, a translocation t(3;8) has been observed in a case of hereditary renal carcinoma (Drabkin *et al.*, 1985). High resolution karyotypes of human bladder transitional cell carcinomas have revealed putatively specific markers, including an isochromosome or deletion of the short arm of chromosome 5, a deletion from chromosome 13, trisomy of chromosome 7, monosomy of chromosome 9 (Gibas and Sandberg, 1984; Gibas *et al.*, 1986) as well as duplication of the short arms (p) of chromosomes 1 and 3, deletion of the long arm of 6, deletion or isochromosome of 8p, deletion of 11p and trisomy 20 (Atkin and Baker, 1985a, b; Fearon *et al.*, 1985; Babu *et al.*, unpublished). The deletion of 11p was associated with a very poor prognosis. The major change observed in renal carcinoma involves the short arm of chromosome 3 (Berger *et al.*, 1986; Kovacs *et al.*, 1987), possibly associated with a putative suppressor gene (see below). Monosomy 14 and loss of Y chromosomes also occurred in many renal tumours (Berger *et al.*, 1986), whereas prostatic adenocarcinomas characteristically show loss of chromosome 10 or changes in the long arm of chromosome 10 (Atkin and Baker, 1985a, b).

### *Recessive oncogenes*

These genes are implicated in rare familial cancers in which the inherited deletion or disablement of one copy of the gene confers a strong predisposition to the development of tissue-specific tumours (Klein, 1987). This is the case in retinoblastoma, in which there is loss of chromosome 13q, in Wilms' tumours, which show loss of chromosome 11p (Knudson, 1985), in small cell carcinoma of the lung and familial renal tumours, in which there is a 3p deletion (Naylor *et al.*, 1987), and in some bladder tumours, which show a deletion of chromosome 11p (Fearon *et al.*, 1985). The gene which is deleted in retinoblastoma patients has now been isolated and is known as the RB gene. The RB protein is found in the nucleus, where it binds to DNA and appears to have a critical role in restricting cellular proliferation. An RB protein with a deletion of a domain of 35 amino acids thought to be necessary for RB function has been described in bladder cancer (Linzer, 1988).

### *Future studies*

Molecular studies of urological cancers have been limited to date. A large number of known oncogenes have not yet been examined in these cancers, and techniques such as differential hybridisation analysis of DNA to determine the role of genes present in cancers versus normal tissue, or in metastatic versus non-metastatic tissue, are in their infancy (Schalken *et al.*, 1988). It is clear from experimental studies that the determination of the genesis of tumours and their evolution will require an understanding of the complex interactions between different types of oncogenes, growth factors and their regulators. To date the only finding with prognostic significance for bladder cancer has been the overexpression of the EGF receptor. However, there is room for optimism, since studies of mutations in the *N-ras* and *Ki-ras* genes have shown very strong correlations with the presence of acute myeloid leukaemia and pancreatic carcinoma respectively, and mutations in *Ki-ras* actually occur in precancerous lesions of the colon (Bos, 1988). Future studies may use techniques which detect these mutations as diagnostic tools. The PCR technique can be used directly on clinical specimens, including epithelial cells in urine samples (Gasparini *et al.*, 1988), as well as on archival, formalin fixed tissue (Shibata *et al.*, 1988), removing any artefacts which may accompany the use of tumour models. The use of this technique will allow rapid accumulation of pertinent data and significant diagnostic or prognostic correlations for urological cancers may be revealed. Alternatively, the altered protein structures encoded by mutated oncogenes may be used to raise monoclonal antibodies for the detection of specific tumour determinants or to monitor drug resistance.

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# Validation of a Self-administered Urological Questionnaire

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Summary—Self-administered questionnaires are widely used in clinical practice and as an aid to research. However, their reliability as a means of eliciting symptoms of urological disease has not been established.

A questionnaire designed to elicit symptoms of urological disease was validated in 120 patients (36 out-patients, 27 in-patients and 57 community patients). All found the questionnaire acceptable and the completion rate was 99%. Only 3 of 648 answers were changed on the test-retest analysis. Consistency, as assessed by a comparison of responses by clinician and patient, was satisfactory in 11 of 15 questions relating to urological symptoms and the questionnaire successfully identified a high risk group of patients from the community requiring further urological evaluation.

The need to include results of a preliminary validation study when reporting results obtained by a self-administered questionnaire is emphasised.

Self-administered questionnaires and computerised methods of history taking are now widely used by physicians and surgeons in the out-patient clinic and have been shown to be an efficient method of information retrieval (Hall, 1972; Gumpel and Mason, 1974; Inui *et al.*, 1979). In addition, they are frequently used as an aid to research and may be used as a method of identifying high risk groups when screening for disease (Wilcock, 1979; Mann *et al.*, 1983). However, self-administered questionnaires are rarely tested statistically for the reliability or validity of the historical information obtained (Pecoraro *et al.*, 1979). Without such validation, results and conclusions may be questioned.

As part of a screening programme for bladder cancer, we constructed a self-administered questionnaire specifically designed to elicit symptoms of urological disease. We report the application of a simple and satisfactory validation system to this questionnaire (Chisholm *et al.*, 1985).

## Patients and Methods

The questionnaire (Fig.) was given to 120 male patients over the age of 60 years; 36 were new referrals to the out-patient clinic, 27 were in-patients with known urological pathology and 57 were patients visiting a local health centre with an unrelated problem. All completed the questionnaire before being seen by the clinician and all but 2 questions were answered by indicating "yes", "no" or "not sure".

In 82 patients (28 out-patients, 17 in-patients and 37 community patients), the questionnaire responses were compared with those obtained by a clinician conducting a routine interview, using his normal method of history taking and having no knowledge of the patient's written responses. The kappa statistic was calculated to adjust for the contribution of chance agreement; a value of 1.0 is equivalent to total agreement, −1.0 total disagreement and a value of zero corresponding to chance agreement alone (Spitzer and Fleiss, 1974; Koran, 1975).

Reproducibility was assessed using the test-retest method (Del Greco *et al.*, 1987). 18 out-patients were asked to complete the same questionnaire 2 weeks later.

## Results

*Acceptability.* All 120 patients agreed to complete the questionnaire.

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Name ................................................Age ......Date of birth ..............

Firstly, some questions about yourself:

During your working life, have you ever worked with:
- chemicals?
- dyes?
- rubber?
- leather?

Have you ever had treatment for high blood pressure?
Have you ever had sugar diabetes?
Have you ever had an operation on your kidney?
Have you ever had an operation on your bladder?
Have you ever had an operation on your prostate gland?
Have you ever had a cystoscopy? (A telescope examination of the bladder)

Has a doctor ever said you had:
- kidney or bladder stones?
- kidney trouble?
- bladder trouble?
- an infection in your water?
- prostate trouble?

Have you taken an aspirin tablet or a tablet containing aspirin in the last two weeks?
Are you on any medicines, tablets or injections from your doctor?
If yes, what are they:.......................................................................

Next, some questions about symptoms of any water trouble you may have:

| | |
|---|---|
| Do you have any difficulty in passing your water? | (0.56) |
| Does it take you longer to pass your water than it used to? | (0.75) |
| Has your water stream become slower over the last few years? | (0.77) |
| Do you sit down to pass your water? | (0.66) |
| Do you have to strain to pass your water? | (0.80) |
| Do you ever find that you have dribbled into your pants? | (0.76) |
| When you get the feeling you want to pass your water, do you need to go immediately? | (0.71) |
| Do you pass water during the daytime more often than you used to? | (0.87) |
| Do you always have to get out of bed at night to pass your water? | (0.90) |
| If yes, do you have to get up more than once? | (0.94) |
| Do you ever wet the bed at night? | (0.80) |
| Have you noticed any change in the colour of your water recently? | (0.65) |
| Have you ever passed blood in your water? | (0.89) |
| Do you ever get any pain or burning when passing your water? | (0.81) |
| Have you had any recent pain in your kidney area? | (0.57) |

Finally, some questions about smoking:

Do you smoke at present?
If not, have you ever smoked in the last 25 years?
If you are a smoker or have smoked in the past, what is the most you have ever smoked?
......cigarettes per day
......cigars per day
......ozs tobacco per week

Thank you very much for answering these questions.
IF YOU HAVE ANY QUESTIONS, PLEASE ASK THE NURSE OR DOCTOR

**Fig.** Questionnaire used in study (kappa statistics in brackets).

*Feasibility.* The completion rate was 99% of all questions; 6 patients admitted to requiring help from a friend or relative.

*Reproducibility.* Three of 648 answers were changed, 2 relating to symptoms and 1 to epidemiology.

*Consistency.* The kappa values for the 15 questions relating to urological symptoms are shown in brackets in the Figure.

*Applicability.* Of questions relating to symptoms, 47% were answered positively in the in-patient group, 38% in the out-patient group and 19% in the community group (Table 1). The number of positive responses given by each patient is shown in Table 2.

## Discussion

This study demonstrates that a self-administered questionnaire can be used to elicit symptoms of

**Table 1** Distribution of Responses to Symptom Questions

| | *No. of responses* | | | |
|---|---|---|---|---|
| | *Yes (%)* | *No (%)* | *Not sure (%)* | *Total* |
| In-patients | 191 (47) | 199 (49) | 15 (4) | 405 |
| Out-patients | 200 (38) | 290 (55) | 35 (7) | 525 |
| Community patients | 161 (19) | 669 (78) | 25 (3) | 855 |

**Table 2** Number of Positive Responses to Symptom Questions

| | *No. of positive responses/patient* | | |
|---|---|---|---|
| | *3 or less (%)* | *3 to 5 (%)* | *6 or more (%)* |
| In-patients | 2 (7) | 6 (22) | 19 (71) |
| Out-patients | 6 (17) | 14 (40) | 15 (43) |
| Community patients | 38 (67) | 8 (14) | 11 (19) |

urological disease. The patients found the questionnaire acceptable, there was good compliance and most questions were answered. Reproducibility is improved by using precise words and avoiding ambiguous terms (Collen *et al.*, 1969; Pecoraro *et al.*, 1979) and was shown to be satisfactory for this questionnaire.

Questionnaire design is important. Misinterpretation of written questions is common (Helsing and Comstock, 1976; Del Greco and Walop, 1987) and validation of a questionnaire attempts to confirm that the patient's understanding of a question is the same as that of the doctor. Answers to questions with a kappa value of less than 0.75 must be interpreted with reservation. Providing the option of responding "not sure" may prevent some inappropriate answers.

Urological symptoms are common over the age of 60 years, both in men with known or suspected urological disease and in men without known disease. This questionnaire successfully identified a high risk group of patients requiring further evaluation; 11 patients without known symptoms (19%) gave 6 or more positive answers to the 15 questions relating to urological symptoms. After assessment by the general practitioner, 5 were thought to require further investigation in the urology department and 4 proceeded to prostatectomy.

This self-administered questionnaire provides a simple, convenient and efficient means of obtaining clinical information, may highlight symptoms that a patient would otherwise not disclose at interview and provides a satisfactory method of eliciting symptoms of urological disease. Such questionnaires can be regarded as reliable only after a preliminary validation study has been performed.

Our questionnaire is now being used in conjunction with a community screening programme for bladder cancer and we hope to report the results of this study within the next year.

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# Pyelo-intestino-cutaneous Conduit in the Treatment of Renal Carcinoma of Solitary Kidneys

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Summary—A pyelo-intestino-cutaneous conduit, either by colonic or ileal segment, was used successfully in 4 patients with urothelial carcinoma affecting a solitary kidney. Primary healing was good but involved the risk of stricture formation. During the follow-up period (10–48 months), repeated endoscopic check-ups were easily performed through the conduit, enabling coagulation of recurrent tumour growth. Two patients are still alive and well; 2 are dead.

The treatment of urothelial carcinoma affecting both kidneys or the renal pelvis of a solitary kidney presents a great surgical problem. Open local excision (Bazeed *et al.*, 1986), transpelvic or ureterorenoscopic electroresection of tumours (Colston and Arcadi, 1955), repeated pyelectomy with pyeloplasty (Firstater, 1960) or renal pelvic resection with transplantation of a free peritoneal patch to the pelvic defect have been proposed (Thüroff *et al.*, 1981; Bazeed *et al.*, 1986). Further approaches include nephroureterectomy, extracorporeal pelvic resection, autotransplantation of the kidney to the pelvic cavity with urinary diversion to the skin using an isolated ileal loop (Henriksson *et al.*, 1984) and the use of intestinal segments to construct a pyelocutaneous conduit (Pyrah, 1957, Prout *et al.*, 1963). The conduit enables endoscopic control and treatment of recurrent renal pelvic or caliceal tumours.

We report 4 patients with a pyelocutaneous conduit constructed from a colonic segment in 3 cases and an ileal segment in 1.

## Patients and Methods

A retrospective study was conducted on 4 patients operated on for urothelial tumours affecting a solitary kidney (3 patients) or a functioning solitary kidney (1). Clinical data are presented in the Table. Three patients had an extensive urothelial carcinoma which had required cystoprostatectomy and contralateral nephroureterectomy at an earlier stage of the disease. In 1 case the function of the contralateral kidney was severely compromised.

## Results

The location of urothelial carcinoma in each patient is presented in the Table. Operative treatment consisted of ureterectomy and subtotal renal pelvic resection followed by construction of a pyelocutaneous ileal or colonic conduit (Fig.). During the follow-up period (10–48 months, mean 22), endoscopic check-ups with biopsy were performed through the conduit at 3-monthly intervals. All but 1 patient had recurrent tumour growth which was treated by electrical or laser coagulation. A relative stricture of the pyelocolic anastomosis was observed in 2 patients (nos 2 and 3). Discission of the strictures was performed successfully with an optic urethrotome (Winter Ibe), thus enabling pyeloscopy and local treatment. Two patients have since died of carcinoma. One patient, who had impaired renal function prior to surgery, developed metabolic acidosis which is managed medically. The other has a slightly elevated serum creatinine concentration but is otherwise well.

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**Table** Clinical Data

| *Patient* | *Age (years)* | *Sex* | *Location of carcinoma* | *Histological grade* | *Operative method* | *Duration of follow-up (months) (status)* |
|---|---|---|---|---|---|---|
| 1 | 66 | M | Pelvis of left (solitary) kidney | 3 | Ileal conduit | 48 (several recurrences, cancer death) |
| 2 | 70 | M | Pelvis, lower calix of left (solitary) kidney | 2 | Colonic conduit | 16 (1 recurrence, alive) |
| 3 | 60 | M | Pelvis, middle and upper calix of right (solitary) kidney | 2 | Colonic conduit | 14 (no recurrence, alive) |
| 4 | 72 | M | Pelvis of right (solitary) kidney | 2 | Colonic conduit | 10 (several recurrences, cancer death) |

## Discussion

Transitional cell carcinoma is often multifocal. This is due either to a uniform sensitivity of the urothelium to a neoplastic stimulus (Schellhammer and Whitmore, 1976) or to implantation of exfoliated tumour cells on the urothelial lining surfaces (Boreham, 1956). Transitional cell carcinoma of the renal pelvis constitutes 5 to 10% of all renal carcinomas; the contralateral renal pelvis and ureter are involved in 1 to 5% of cases (Grabstald and Whitmore, 1971; Babaian and Johnson, 1980; Frischer *et al.*, 1985). Shinka *et al.* (1988) reported the incidence of secondary upper tract tumours after diagnosis and treatment of bladder carcinoma to be 1.1% in the general population and 13.2% in dye workers. When both kidneys are affected, or the contralateral kidney has already been removed, the urologist has to decide between adopting an aggressive surgical approach with haemodialysis or allotransplantation, or kidney-preserving surgery combined with a pyelocutaneous conduit.

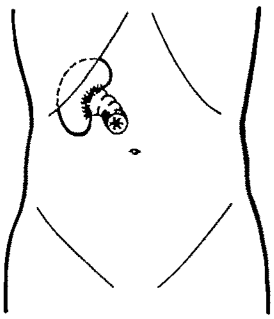

**Fig.** Schematic illustration of pyelo-intestino-cutaneous conduit either by colonic or ileal segment after subtotal pelvic resection.

Various bowel segments have been used as substitutes for portions of the urinary tract (Pyrah, 1957; Prout *et al.*, 1963). Recently, subtotal pelvic resection followed by a pyelocutaneous conduit, either by isolated ileal or colonic segment, has been successfully used in our clinic in those rare cases where uroepithelial carcinoma affects both kidneys or the pelvic region of a solitary kidney (Rannikko and Oravisto, 1986; Lindell and Lehtonen, 1988). These operations involve no difficult technical problems. Primary healing of the pyelointestinal anastomosis is good, even if there seems to be a risk of subsequent stricture formation.

Local recurrences are typical of all urothelial carcinomas. In the present series, 2 patients had several recurrences in the remaining pelvicaliceal region. The pyelocutaneous bowel segment enables repeated endoscopic check-up of this aggressive, multifocal carcinoma, and recurrent tumour growth can be controlled by coagulation.

Our findings confirm the possibility of an isolated bowel segment being used as a pyelocutaneous conduit after subtotal renal pelvic resection. This type of conservative, kidney-preserving surgery, combined with modern endoscopic procedures, enables recurrent tumours to be controlled and merits consideration when deciding on treatment in these extremely serious situations.

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# Antegrade Ureterolitholapaxy in the Treatment of Obstructing or Incarcerated Proximal Ureteric Stones

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Summary—Extracorporeal shockwave lithotripsy (ESWL) and retrograde ureterorenoscopy (RU) have transformed the management of ureteric calculi. Nevertheless, patients with obstructing proximal ureteric calculi are not suitable for ESWL or RU.

From January 1986 to September 1988, 17 patients with fixed upper ureteric stones underwent antegrade renoureteroscopy and percutaneous surgery. The technique was effective in removing incarcerated proximal ureteric calculi: all patients were stone-free at follow-up 3 months later.

Proximal ureteric stone disease remains a problem with no simple solution despite the recent advances in extracorporeal shockwave lithotripsy and the use of sophisticated endourological instruments.

In the case of a stone which is obstructing, or remains blocked for over a month in the ureteric wall, ESWL is not a viable procedure because of the lack of space necessary for stone disintegration (Gumpiger *et al.*, 1985).

Even retrograde ureterorenoscopy does not usually achieve total clearance of calculi, since difficulties in manipulation may lead to damage (Fuchs *et al.*, 1986). The percutaneous approach, using the ureteroscope via an antegrade access, seems a better solution in the treatment of obstructing or incarcerated proximal (down to the iliac crest) ureteric stones.

## Patients and Methods

Between January 1986 and December 1988, 157 patients (102 men and 55 women, mean age 44 years) were subjected to percutaneous lithotripsy; 17 of them (10 men and 7 women, mean age 38 years) had had a fixed proximal ureteric stone without evidence of progression for more than 1 month. After an unsuccessful attempt to push the stone into the renal cavity, patients underwent antegrade ureterolitholapaxy (Figs. 1–3). The ureteric calculi varied in size from 0.9 to 2.2 cm. We performed 15 punctures in the middle calix and 2 in the lower posterior calices; in 7 patients it was necessary to proceed by intercostal access and in 10 cases access was subcostal.

The operations were performed under local anaesthesia by regional infiltration (mepivacaine 2‰, 20–40 ml, with the support of a narcotic and atropine) and sedation with flunitrazepam continuous i.v. infusion (Anselmo *et al.*, 1987). The upper urinary tract was visualised and dilated (when possible) by a contrast medium injected through a ureteric catheter (6–8 F) previously positioned by transurethral access close to the stone, in order to perform the puncture under fluoroscopic control, coaxial with the most appropriate calix. During lithotripsy the ureteric catheter also prevents fragments from falling down the ureter.

Before the operation 8 patients, 3 of whom had pyonephrosis, were subjected to repositioning of a percutaneous nephrostomy left in place for 15–30 days (Fig. 4). In the case of intercostal access an echograph is essential in order to avoid pleuro-pulmonary, hepatic or splenic lesions.

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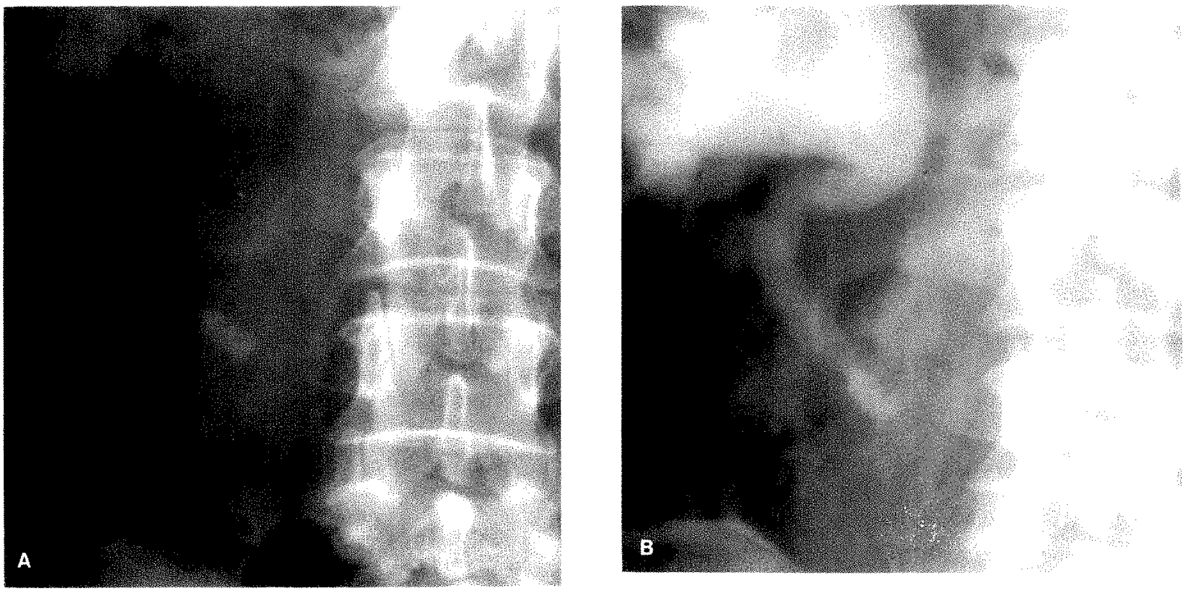

**Fig. 1** (A) Plain film. (B) Intravenous urogram.

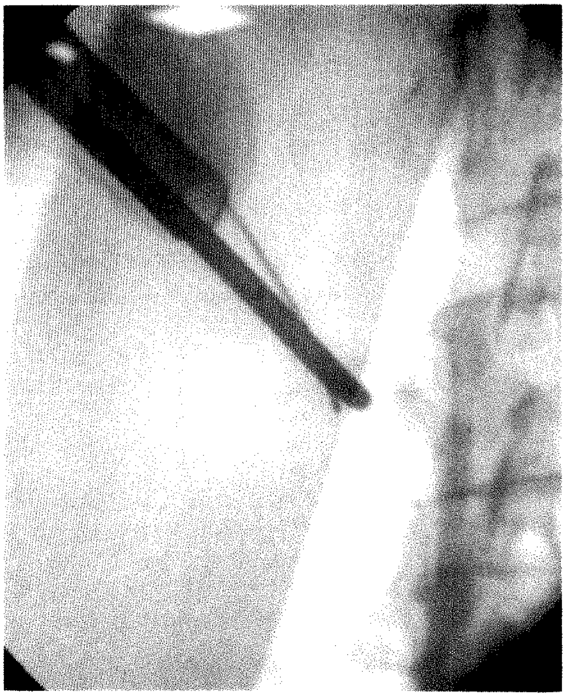

**Fig. 2** Antegrade ureterolitholapaxy.

Dilatation is performed up to 26F by Alken telescopic dilators. A rigid 11F ureteroscope is inserted through the nephroscope sheath, pushing it under direct vision into the ureter to reach the stone (Fig. 5). Either a Seldinger guide or a small angiographic catheter can be pushed along the ureter in order to make manipulation easier.

In all cases we applied ultrasonic lithotripsy using grasp forceps to remove the resulting fragments. After removal of the stone, a 24F nephrostomy is left in place until X-ray evidence confirms complete clearance of fragments. If there remains any suspicion of lesions or perforations, a ureteric catheter is positioned as far as the bladder and left *in situ* for 7 days.

## Results

No significant bleeding occurred during the procedure and no major complications were encountered; 16 patients were completely cleared of stones in a single session. In 1 patient the procedure had to be interrupted because of a small ureteric perforation which was treated by positioning a ureteric stent, left in place for 7 days, and also leaving a nephroscopic drain in the percutaneous tract; this was used later to extract residual stone fragments.

After 3 months all patients were screened by X-ray; none had residual fragments or dilatation of the axis treated.

## Discussion

In the last few years, treatment of proximal ureteric

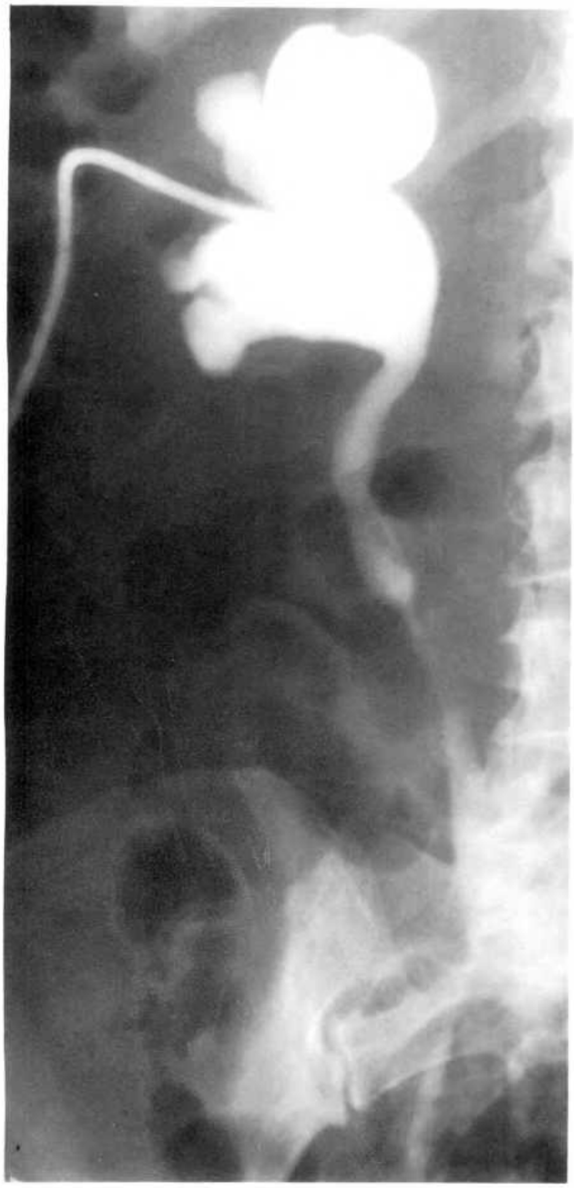

**Fig. 3** Post-treatment nephrostography.

stone disease has undergone remarkable changes following the development of extracorporeal lithotriptors and other sophisticated endourological instruments (Goodfriend, 1984). The choice of treatment depends mainly on the position and size of the stone and on its relationship with the ureter (Sanseverino *et al.*, 1988).

A large proximal ureteric stone, blocked for over a month in the urinary tract, cannot be treated by retrograde access. Extracorporeal shockwaves are unsuitable owing to the lack of room for expansion. Retrograde ureterorenoscopy is therefore inadequate if applied to the proximal ureter because the distance covered by the instrument makes manipulation of the stone difficult and there is a high risk of perforating the urinary tract. Moreover, the ureteric section under the stone either maintains its normal diameter or becomes stenotic because of inflammation or spasm. Anatomical conditions thus prevent sufficient water cooling during ultrasonic treatment and abnormal heat could damage the ureter. It is also possible that during manipulation some calcareous fragments might enter the excretory cavities. This method, therefore, when applied to blocked and obstructing proximal ureteric calculi, is invasive and has a high morbidity rate.

In patients with abnormal dilatation or dysfunction of the upper urinary tract, or affected by hydropyonephrosis, any intervention should be preceded, in our opinion, by the repositioning of a translumbar percutaneous nephrostomy in order to ease any obstruction and to obtain "nephrological reanimation" of the relevant axis; renal function should be assessed later. The application of antegrade ureteroscopy makes it possible to avoid or reduce to a minimum any damages to the ureter, bearing in mind that the excretory axis above the stone is dilated and thus facilitates progression of the instrument. Heat lesions are also avoided while using ultrasound as a result of the irrigation related to the anatomical conditions and to the water exchange afforded by the nephroscope sheath, which acts as an Amplatz sheath. The short duration of the procedure reduces to a minimum any discomfort to the patients.

The procedure should always be preceded by an attempt to push the stone into the renal pelvis; if successful it is possible to apply less invasive methods for stone clearance. In the present series this manoeuvre failed because of ureteric oedema or total incarceration of the stones.

We believe, as do Gumpinger *et al.* (1985), that proximal ureteric obstructing stones which are blocked for over a month should be treated by antegrade ureterolitholapaxy as the method of first choice, this being the best alternative to ureterolithotomy.

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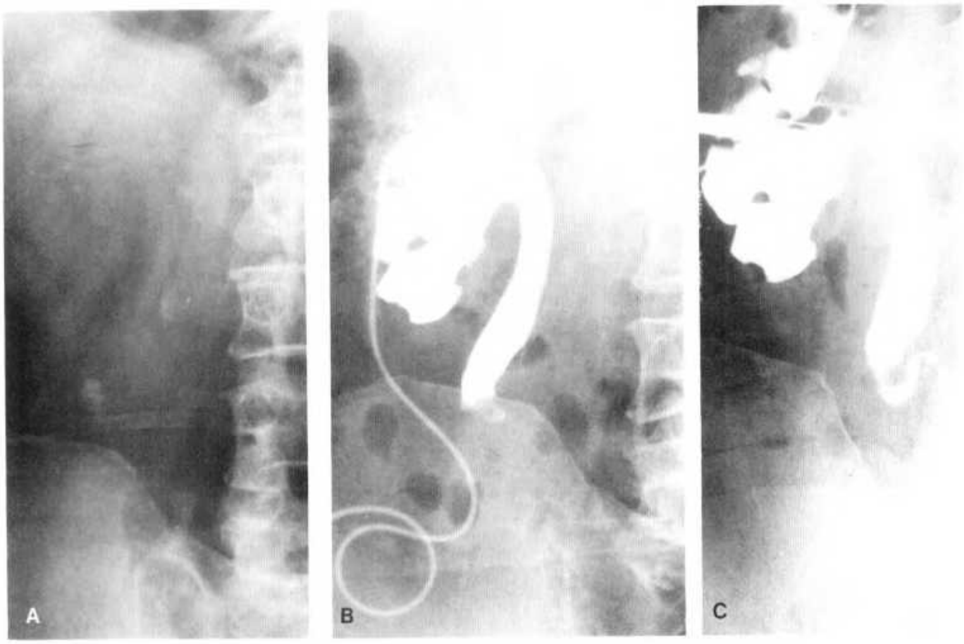

**Fig. 4** (A) Plain film. (B) Pre-operative nephrostography. (C) Post-operative nephrostography.

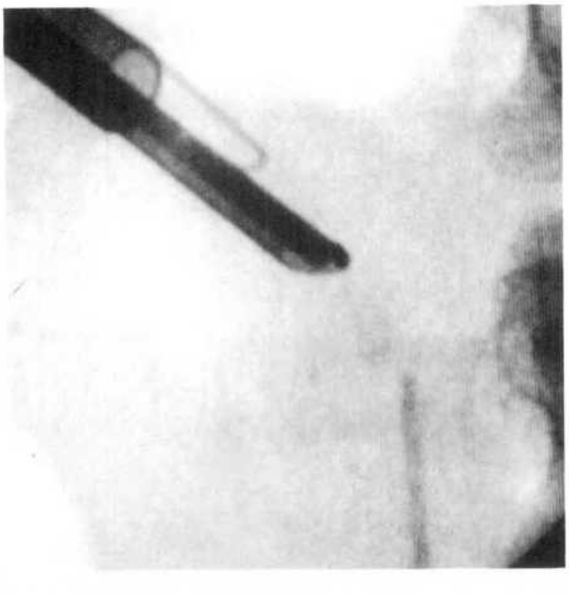

**Fig. 5** Antegrade ureterolitholapaxy.

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# Transurethral Ureterorenoscopic Lithotripsy and Retrieval of Ureteric Calculi under Local Anaesthesia and Sedation

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Summary—Under strict indications, ureterorenoscopic (URS) lithotripsy was used to treat ureteric calculi in 61 patients under local anaesthesia and sedation in a 2-year period ending November 1988. Assessments of success and discomfort of the procedure were made. Stone retrieval was accomplished in 48 patients (78% success rate) and a mean pain score of 6 was recorded in a scale from 0 to 10. It was concluded that performing URS under local anaesthesia is an acceptable alternative.

Transurethral ureterorenoscopic lithotripsy and retrieval of ureteric calculi has become an established procedure in recent years (Ford *et al.*, 1983, 1984). The results reported in the literature were achieved in patients treated under spinal, epidural or general anaesthesia (Ford *et al.*, 1984; El-Kappany *et al.*, 1986; St C. Carter *et al.*, 1986; Coptcoat *et al.*, 1988; Kostakopoulos *et al.*, 1989). We studied the feasibility of performing this procedure under local anaesthesia and sedation.

## Patients and Methods

Patients with ureteric calculi which were obstructing, causing persistent pain or making minimal progression towards the bladder during a 3-month observation period were admitted for surgical treatment. In a 2-year period ending November 1988, 111 patients were admitted and 61 had their ureteric calculi removed by ureterorenoscopic retrieval under local anaesthesia and sedation (Table 1). URS lithotripsy and retrieval was routinely performed under local anaesthesia and sedation unless the patient insisted on having general anaesthesia. The patients were given diazepam 10 mg orally 30 min pre-operatively and were put in the lithotomy position with the head of the table raised about 20°; 2% lignocaine gel was instilled into the urethra for 3 min before instrumentation. An X-ray image intensifier and an ultrasonic and electrohydraulic lithotriptor were in position and ready for use if required. Cystoscopy was performed so that the ureteric orifice and the lower part of the ureter could be dilated. A ureteric balloon dilator (5 mm × 5 cm and 6 mm × 5 cm balloon) or polyethylene ureteric dilators (up to 14 F) over a guidewire and under vision through a renoscope in the bladder were used. A 12.5 F Perez-Castro ureterorenoscope (Storz) was introduced transurethrally into the ureter up to the site of the stone, which was retrieved intact or after lithotripsy. On completion of the procedure, the time taken was

**Table 1** Details of Patients

| *Procedure/outcome* | *Male* | *Female* |
|---|---|---|
| URS (LA) | 20 | 41 |
| URS (GA) | 14 | 7 |
| PCNL (push + pull) | 5 | 2 |
| Ureterolithotomy (without URS) | 2 | 0 |
| Spontaneous passage | 12 | 4 |
| Refused surgery | 2 | 0 |
| Defaulted admission | 1 | 1 |
| Total | 56 | 55 |

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noted and the patient was asked to mark the degree of pain on a score of 0 to 10 (0 = no pain; 10 = extreme unbearable pain).

## Results

A total of 61 patients—20 male and 41 female aged 22 to 82 years (mean age 43) were treated by this procedure under local anaesthesia and sedation. The ureter was divided into 3 levels in relation to the sacroiliac joint (Fig.), so that the upper, middle and lower ureter were proximal to, crossing the joint and distal to the joint respectively. This scheme of ureteric division has some practical significance since the segment of the ureter crossing the sacro-iliac joint is the most difficult region to negotiate with the ureterorenoscope. The distribution of the ureteric stones is shown in the Figure. The mean stone size was 10.4 × 5.5 mm in the successful group and 10.3 × 6.3 mm in the failure group (Table 2). The mean pain score and mean operating time were 6.1 and 57.5 min respectively in the successful group and 5.7 and 47.9 min in the failure group (Table 3). The overall success rate was 78% (Table 4). Twelve patients, including 1 converting to general anaesthesia in the second attempt, required the procedure twice for complete retrieval of stone fragments. The procedure failed to retrieve stones in 13 patients (22%), 5 of whom required further surgery (pyelolithotomy 1, ureterolithotomy 4); 4 patients defaulted follow-up and the rest had spontaneous passage of stones.

**Table 2** Mean Stone Size

| | *Largest dimension* × *(mm)* | *Smallest dimension* *(mm)* |
|---|---|---|
| Successful | 10.4 (5–23) | 5.5 (3–12) |
| Failed | 10.3 (5–25) | 6.3 (3–10) |

**Table 3** Mean Pain Score and Mean Operating Time

| | *Successful retrieval* | *Failed retrieval* |
|---|---|---|
| Mean pain score (out of 10) | 6.1 (0–8) | 5.7 (0–9) |
| Mean operating time (min) | 57.5 (10–180) | 47.9 (20–90) |

**Table 4** Success Rates

| | |
|---|---|
| Upper ureter | 9 (16) = 56% |
| Middle ureter | 7 (8) = 87% |
| Lower ureter | 32 (37) = 86% |
| Total | 48 (61) = 78% |

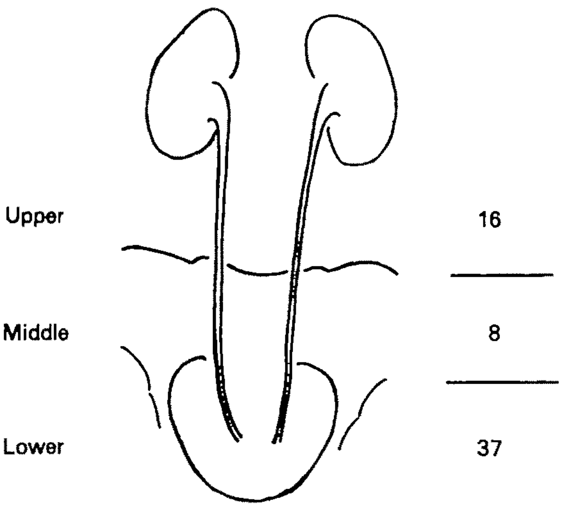

**Fig.** Distribution of ureteric stones.

## Discussion

The overall success rate of 78% stone retrieval under local anaesthesia and sedation compares favourably with success rates when the procedure was carried out under general anaesthesia (Ford *et al.*, 1984; St. C. Carter *et al.*, 1986; Coptcoat *et al.*, 1988; Kostakopoulos *et al.*, 1989) or spinal, epidural and general anaesthesia (El-Kappany *et al.*, 1986). The reported success rates ranged from 64 to 88%. Our failure was due to technical problems and in reaching the stones rather than patient discomfort, because the success rate was highest when the stone was in the lower ureter (86%). Just over half of the stones in the upper ureter were removed. Surprisingly, the size of the stone did not appear to influence the outcome of the procedure since the stones were comparable in size in both the success and failure groups.

Despite the large size of ureteric stones encountered in this series, the procedure was well tolerated by the patients, with a mean pain score of 6. Moreover, of 12 patients who required a repeat procedure, only 1 opted for general anaesthesia.

We concluded that transurethral URS lithotripsy and retrieval of ureteric stones under local anaesthesia and sedation is feasible and acceptable. This useful alternative allows greater flexibility when general anaesthetic operating sessions are limited or when the patient load is great.

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# Vesicoureteric Reflux in the Adult Male

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Summary—The main prevalence of vesicoureteric reflux (VUR) is in the adult female population. Although recognised as a clinical entity in adult males, little detailed information is available on this subject. A retrospective analysis was carried out on the results of 1519 consecutive videocystometrograms performed on male patients. VUR had an overall incidence of 8.6% within this population, with a range of 5.1% in patients with normal urodynamics to 15.6% in those with detrusor-sphincter dyssynergia. The common denominator between VUR and urodynamic measurement appears to be the generation of high intravesical pressures. These findings suggest that VUR is not uncommon in the male population, is usually asymptomatic and should respond to the treatment of any underlying bladder abnormality.

Vesicoureteric reflux occurs mainly in women in the adult population and is well recognised in children, where it can be subdivided into primary and secondary categories depending respectively on the absence or presence of recognised contributory pathology. A review of the literature reveals a dearth of information relating to this problem in adults and in particular its incidence in men (Lipsky and Chisholm, 1971; Amar and Das, 1985).

Although there has been debate over the indications for and advantages of medical versus surgical treatment in the long-term management of primary VUR (Senoh *et al.*, 1977; Weston *et al.*, 1982; Neves *et al.*, 1984), it is now well established from studies in childhood (Allen, 1985; Homsy *et al.*, 1985; Noe, 1985) and adult VUR (Amar and Das, 1985) that the pharmacological correction of underlying bladder dysfunction could potentially ameliorate associated symptoms and should therefore precede any attempts at surgical correction of secondary reflux.

The aim of this retrospective study of clinical and urodynamic data was to document the prevalence of VUR in adult males.

## Patients and Methods

The results of 1519 consecutive videocystometrograms (VCMGs) performed on male patients at the Middlesex Hospital were analysed retrospectively (mean age 55.96 ± 1.02 years). Fast fill (>100 ml/min) VCMG was carried out using the technique described by Bates *et al.* (1970). Statistical analysis was carried out on an Amdal mainframe computer using the statistical package (SPSSX, version 2.1). On the basis of urodynamic assessment this population was further divided into the following subgroups: normal 176 (11.6%), unobstructed primary detrusor instability 482 (31.7%), stable outflow obstruction 154 (10.1%), detrusor instability with outflow obstruction 443 (29.2%), neuropathic detrusor 187 (12.3%) and detrusor/sphincter dyssynergia 77 (5.1%).

VUR was documented in the course of VCMG during either the filling or voiding phase and if present usually occurred during both. The diagnosis of VUR was made if contrast was noted to extend retrogradely up the ureter for more than 1 cm.

## Results

The overall prevalence of VUR in the adult males was 8.6%. Further analysis of the subgroups in this population revealed that the greatest incidence of reflux occurred in patients with detrusor/sphincter dyssynergia (15.6%). All forms of bladder dysfunction were associated with a significantly higher

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incidence of VUR when compared with patients with no apparent urodynamic abnormality (Table 1). Detrusor instability and bladder outlet obstruction appeared to have an additive effect, with VUR being commonest in patients with a documented neurological abnormality. A review of mean filling and voiding pressures (Table 2) confirmed this impression. Although filling pressures were high in most of the groups, an additional factor appeared to be that of associated bladder outlet obstruction. A higher incidence of VUR accompanied stable obstruction than idiopathic detrusor instability, with a further increase in the incidence of reflux in patients with a combination of the 2 factors and in patients with neuropathic detrusor dysfunction. The magnitude of voiding pressure did not appear to be correlated with the prevalence of VUR.

The incidence of loin pain was 16.03% in patients with VUR and 7.92% in the non-refluxers, a statistically significant difference ($P<0.01$). There was a history of recent urinary tract infection in 16.8% of the patients with VUR and in 18.9% of the non-refluxers (not statistically significant) (Table 3). It should, however, be borne in mind that patients were being investigated because of urinary tract dysfunction and a number of these patients had other significant risk factors which might predispose them to the subsequent development of urinary tract infection.

**Table 1** Prevalence of Vesicoureteric Reflux in Urodynamic Subgroups

| | *Vesicoureteric reflux* | |
|---|---|---|
| *Bladder function* | *No.* | *%* |
| Normal | 9 | 5.1 |
| Primary detrusor instability | 35 | 7.3 |
| Stable outflow obstruction | 14 | 9.1 |
| Unstable outflow obstruction | 44 | 9.9 |
| Neuropathic | 27 | 14.4 |
| Detrusor-sphincter dyssynergia | 12 | 15.6 |
| Total | 131 | 8.6 |

There was no apparent association between unilateral or bilateral reflux and the underlying bladder dysfunction in any of these groups. In all patients reviewed in this study VUR was confined to the ureter.

## Discussion

Primary VUR is often associated with loin pain on micturition and is known to be important in the pathogenesis of recurrent urinary tract infections (Lipsky and Chisholm, 1971). VUR may ultimately lead to renal impairment, depending on the extent of the reflux and associated infection. In the presence of persistent symptoms failing to respond to medical treatment or deteriorating renal function, the role of conservative treatment versus surgery still remains controversial (Senoh *et al.*, 1977; Neves *et al.*, 1984). It has been suggested that surgery has little effect in arresting deteriorating renal function, but is particularly important in the prevention of recurrent infections. Unlike the paediatric experience, adult reflux does not resolve with the passage of time. It is acknowledged that the true incidence of primary VUR is far less common in men than women, with a 1 to 4 ratio reported by Lipsky and Chisholm (1971). However, in 95 patients with primary VUR it was noted that 38 were male and 16 (42%) were asymptomatic (Nativ *et al.*, 1987). A review of the literature, demonstrates that the true prevalence of asymptomatic male VUR is unknown and can only be alluded to by the use of studies such as this, since all reported series have to rely upon reviews of selected symptomatic populations.

It is of note that the data collected in this study reveal a 5.1% incidence of VUR in the subgroup of patients with normal urodynamics; this is likely to be higher than might be expected in the general population since these patients were being investi-

**Table 2** Mean Maximum Filling and Voiding Detrusor Pressures in the Urodynamic Subgroups with Vesicoureteric Reflux

| *Bladder function* | *Mean max. filling pressure ($cm\ H_2O$)* | *Mean voiding pressure ($cm\ H_2O$)* |
|---|---|---|
| Normal | 11.8 (±1.7) | 48.1 (±1.0) |
| Primary detrusor instability | 58.3 (±2.7) | 47.6 (±0.9) |
| Stable outflow obstruction | 13.5 (±3.1) | 73.0 (±3.1) |
| Unstable outflow obstruction | 65.6 (±3.6) | 90.6 (±2.3) |
| Neuropathic | 64.6 (±5.7) | 55.1 (±3.0) |
| Detrusor-sphincter dyssynergia | 58.9 (±10.6) | 53.3 (±4.0) |

**Table 3** Incidence of Loin Pain and Infection in Patients with Vesicoureteric Reflux

| *Bladder function* | *Loin pain (%)* | *Infection (%)* |
|---|---|---|
| Normal | 6 (67) | 3 (33) |
| Primary detrusor instability | 7 (20) | 7 (20) |
| Stable outflow obstruction | 1 (7) | 4 (29) |
| Unstable outflow obstruction | 4 (9) | 5 (11) |
| Neuropathic | 2 (7) | 2 (7) |
| Detrusor-sphincter dyssynergia | 1 (8) | 1 (8) |

**Table 4** Incidence of Loin Pain and Infection According to Bladder Function

| *Bladder function* | *Loin pain (%)* | *Infection (%)* |
|---|---|---|
| Normal | 24 (13) | 49 (27) |
| Primary detrusor instability | 35 (7) | 80 (16) |
| Stable outflow obstruction | 17 (11) | 36 (26) |
| Unstable outflow obstruction | 46 (10) | 70 (15) |
| Neuropathic | 10 (5) | 30 (16) |
| Detrusor-sphincter dyssynergia | 5 (6) | 19 (24) |

gated because of significant symptoms. In this normal subgroup there was a significant incidence of loin pain and recurrent urinary tract infections associated with VUR (Tables 3 and 4). The patients in this series exhibited a clear inter-relationship between VUR and bladder dysfunction (Table 1). Reflux was more common in the presence of associated high maximum filling detrusor pressures (Table 2), as has been reported previously in paediatric practice (Allen, 1985). This association is to be expected since the storage phase occupies most of the bladder's functional life and the pressure rises which are associated with bladder voiding are transient in comparison. Nevertheless, bladder outflow obstruction and high maximum voiding detrusor pressures were also associated with an increased incidence of VUR, suggesting that high voiding pressure might be of pathogenic importance, a finding supported by the observation of an increased incidence of VUR in patients with obstructive prostatic disease (Amar and Das, 1985).

In this study, combined detrusor instability and outflow obstruction resulted in a higher incidence of VUR, with the patients with stable obstruction intermediate in terms of incidence between unstable obstruction and primary detrusor instability. In the presence of neuropathy, intravesical pressure rises can be extremely high, particularly during filling even at low bladder volumes. Not surprisingly, therefore, in this group of patients there was a particularly high incidence of VUR. An additional factor in this situation could be related to the disordered innervation adversely affecting the ability of the trigonal musculature to prevent reflux at the vesicoureteric junction. Maximum filling and voiding detrusor pressures (Table 2) were higher in patients with the greatest incidence of VUR. A true linear relationship was not present, which on reflection is not surprising, since these patients had varying degrees of VUR and the associated resulting "dead space" of the upper tract would tend to act as a capacitance space which could significantly dampen down pressure changes within the bladder.

No previous studies have identified the true prevalence of VUR in an adult male population. The finding that there is a significant correlation with bladder dysfunction raises the possibility that effective treatment of the bladder may, as previously reported, reduce the incidence of VUR (Homsy *et al.*, 1985). A recent study on VUR in a paediatric population documented 2 different types of reflux/bladder dysfunction. One type included bladder instability with powerful voiding contractions of the bladder, whilst the other had poorly contractile bladders but associated over-activity of the urethral sphincters (Griffiths and Scholtmeijer, 1987). The common denominator in both groups of patients was the transmission of high pressures to the upper tract, as in this study.

Videocystometry detects VUR which would otherwise pass unrecognised in patients with bladder dysfunction documented at simple cystometry, since it is often not associated with loin pain or infection. The potential for the chronic transmission of high pressure and infection from bladder to kidney could lead to renal damage. The results reported here support the suggestion that correction of underlying bladder dysfunction should lead to reduction in the degree and incidence of VUR. To assess the potential importance of these findings and their implications in clinical practice, long-term prospective studies need to be carried out in a similar population.

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# Acquired Venous Disease of the Lower Urinary Tract

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Summary—Thrombosis of the vena cava, femoral veins or iliac veins can result in the formation of large collateral veins in the pelvis and retroperitoneum which are often asymptomatic but which may cause severe bleeding and produce major difficulties in urological management. Such abnormalities are a rare cause of urological symptoms but may be difficult to diagnose unless a high index of suspicion is maintained. Three patients are reported who developed significant urological problems as a consequence of acquired venous disease; the use of ultrasound, venography and CT in the diagnosis of this condition is described.

Vascular abnormalities of the urinary tract are uncommon and include congenital haemangiomatous lesions which have been well characterised previously (Chopra *et al.*, 1965; Fuleihan and Cordonnier, 1969; Murray *et al.*, 1986). Venous varicosities of the renal pelvis and ureter have also been described (Gillenwater *et al.*, 1963; Samellas, 1965; Hayashi *et al.*, 1980) and the majority appear to be collateral veins resulting from congenital anomalies of the renal veins or vena cava. Such varices may be found incidentally in up to 6% of patients undergoing renal venography for reasons other than bleeding, and their relationship to haematuria remains uncertain.

The occlusion of any major vein may result both in the formation of collateral veins carrying venous return and also in visceral dysfunction caused by venous hypertension. Obstruction of the vena cava (Missal *et al.*, 1965) can give rise to particular clinical syndromes depending on the site of the blockage. Thus, hepatic damage will predominate if the retro-hepatic segment of the vena cava is affected, but proteinuria will occur if the renal segment is involved. Obstruction of the lower part of the vena cava or the iliac veins can cause marked collateral formation in the retroperitoneum, obturator and perivesical veins (Pagani *et al.*, 1982). It is not well known that such collateral veins can give rise to urological problems. We report 3 patients who developed significant urological problems after thrombosis of the vena cava or iliac veins had produced venous collaterals affecting the lower urinary tract.

## Patients

*Case 1.* A 65-year-old man with symptoms of bladder outflow obstruction was referred for prostatectomy. He gave a history of previously treated unilateral deep venous thrombosis which was not clinically evident at the time of prostatectomy. During the course of endoscopic prostatectomy there was very severe venous bleeding and the patient rapidly became hypotensive and shocked. The procedure was terminated but the patient died soon after. At post mortem examination, one common iliac vein was found to be occluded with huge varicose veins surrounding the bladder base and traversing the prostate; these obviously represented the venous collateral circulation and were inadvertently sectioned in the course of prostatectomy.

*Case 2.* A 17-year-old male was admitted as an emergency, passing blood and clots *per urethram.* At the age of 2 weeks he had developed a cerebral abscess which had required prolonged antibiotic treatment and intravenous fluid therapy via a right femoral line. Routine haematological examination and urine analysis were normal except for the presence of red cells in the urine. Cytological examination showed normal urothelial cells and an IVU was normal. At cystoscopy the right side of the bladder was grossly abnormal and the mucosa over the trigone was elevated by large varicose veins. A 2 mm erythema-

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tous papule on the posterior wall of the bladder was biopsied and histological examination demonstrated numerous thin walled vascular channels.

Ultrasound examination of the venous system demonstrated that the vena cava, common iliac veins, internal iliac veins and left common femoral veins were normal. The right common femoral vein was occluded and Doppler signals, compatible with large collaterals, were observed around the right side of the bladder. A venogram was performed which confirmed occlusion of the right common femoral vein. Marked collaterals were observed passing through the obturator canal and ascending to join enlarged inferior hypogastric body wall branches (Fig. 1). In addition, whilst the left common femoral and left iliac veins were patent, the vena cava was not opacified and all of the venous return was provided by an enlarged ilio-lumbar trunk forming a confluence with a huge hemi-azygos vein which presumably had been mistaken for the vena cava on ultrasound (Fig. 2).

*Case 3.* A 26-year-old man presented with bilateral hydronephrosis. He had previously been diagnosed as having staphylococcal osteomyelitis of the L4/L5 lumbar vertebrae. This had been present for 11 years and had been diagnosed during investigation of suspected Guillain-Barré syndrome and Hodgkin's disease, neither of which was confirmed. He had persisted with a discharging sinus in the loin for several years and bilateral hydronephrosis had been found during recent investigations for back pain. The IVU had also shown a deformed bladder consistent with pelvic lipomatosis (Fig. 3). However, CT showed that large venous collaterals were present around the bladder (Fig. 4) with a huge venous collateral (an enlarged testicular vein) which initially was thought to be an iliac aneurysm arising from the external iliac artery. He underwent cystoscopy, which confirmed the presence of huge varicose veins under the bladder mucosa and around the bladder neck. He also underwent temporary placement of bilateral ureteric stents to relieve the hydronephrosis. The presence of extensive venous collaterals was confirmed on venography (Fig. 5). Unfortunately, he suffered a deep venous thrombosis in the leg following this procedure and required prolonged anticoagulation with warfarin. Venography and CT had been carried out in order to identify the extent of bony sequestrum formation in the lumbar spine and also to

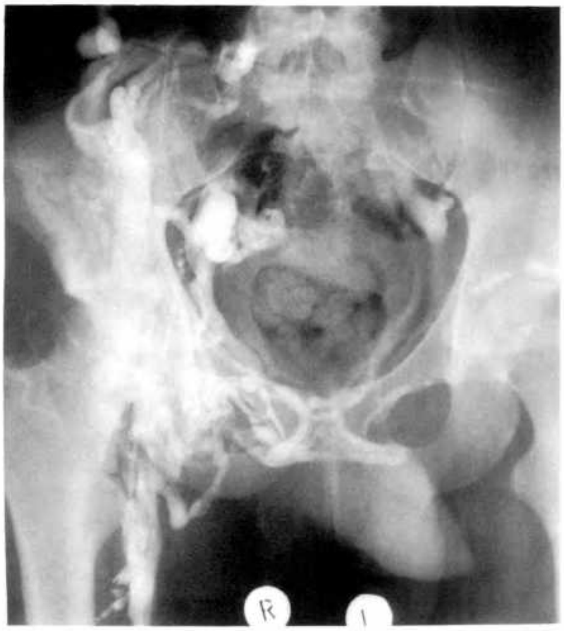

**Fig. 1** Venogram showing obliteration of the right common femoral vein with collateral formation passing through the obturator foramen and around the right side of the bladder and joining retroperitoneal and inferior hypogastric veins (Case 2).

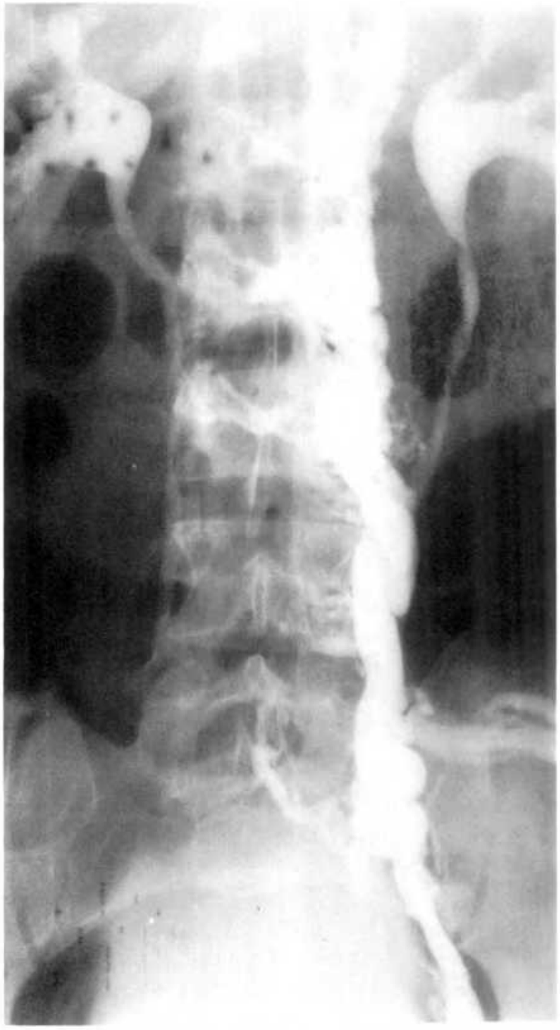

**Fig. 2** Venogram showing the contrast from the left common femoral vein ascending in the ilio-lumbar vein to join a grossly enlarged hemi-azygos vein: no vena cava was demonstrated.

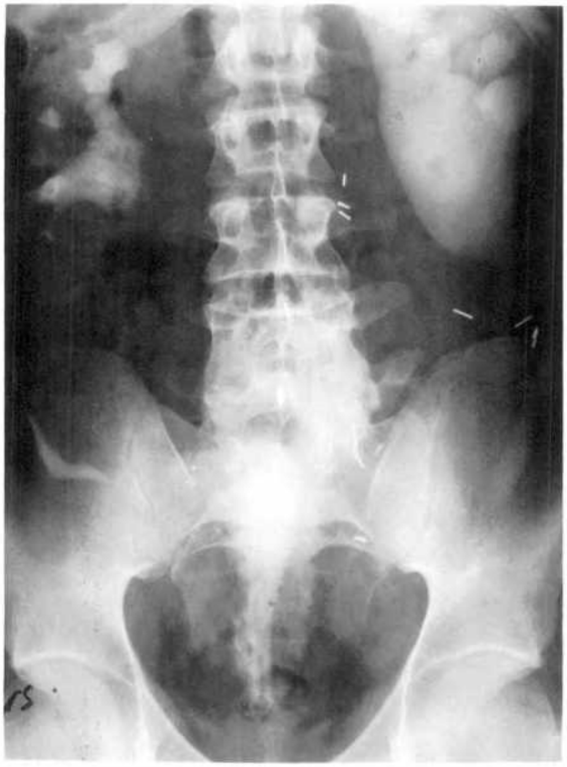

**Fig. 3** IVU showing deformity of the bladder consistent with pelvic lipomatosis (Case 3). The patient had previously undergone bilateral ureterolysis with lateral displacement of the ureters.

confirm possible vena caval compression. A diagnosis was made of extensive retroperitoneal fibrosis secondary to osteomyelitis, compression of the lower part of the inferior vena cava and extensive venous collateral formation. He underwent a left ureterolysis which was performed in conjunction with excision of a bony sequestrum. A right ureterolysis was subsequently performed but it proved impossible to perform a lysis of the vena cava because of dense fibrous tissue, although at a later cystoscopy there appeared to have been marked resolution of the collaterals in the bladder.

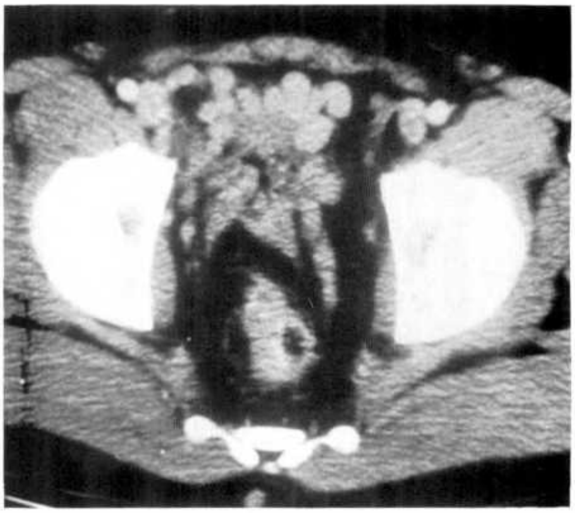

**Fig. 4** CT showing gross enlargement of veins around apex of prostate (Case 3).

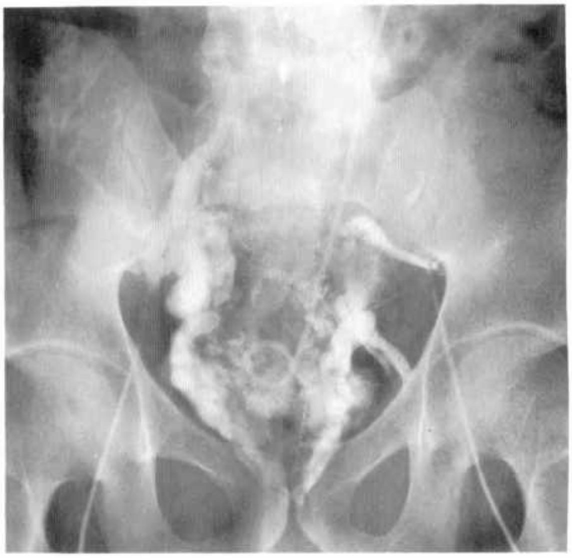

**Fig. 5** Venogram showing marked collateral formation in the pelvis (Case 3).

## Discussion

These 3 patients illustrate the problems that may arise in the lower urinary tract from previous venous thrombosis. Whilst there is little to be found in the urological literature on this topic, we have observed such collateral formation not infrequently in the radiological investigation of patients with previous venous thrombosis affecting the vena cava or iliac veins. The anatomy of these venous collaterals has been described previously in the radiological literature (Pagani *et al.*, 1982). Presumably, only rarely do the collateral veins arising as a consequence of such thrombosis cause clinically evident problems despite the commonplace nature of venous thrombosis.

Congenital haemangiomatous and arteriovenous malformations of the urinary tract usually present with haematuria (Chopra *et al.*, 1965; Fuleihan and Cordonnier, 1969; Murray *et al.*, 1986; Nuova *et al.*, 1986) and are often accompanied by skin haemangiomata. These abnormalities were not present in our patients and from the evidence it seems that the venous varicosities arose after venous thrombosis. There have been previous reports of venous varices affecting the renal pelvis and lower ureter (Gillenwater *et al.*, 1963; Samellas, 1965) and it has been suggested that these arise in conjunction with congenital obstruction of the vena cava or renal veins (Hayashi *et al.*, 1980). However, thrombosis affecting the lower part of the inferior vena cava can also cause marked collateral formation and it has been noted the engorgement of the prostatic venous plexus can cause prostatic symptoms (Missal *et al.*, 1965), whereas vena caval thrombosis of the middle part of the inferior vena cava involving the renal vein can cause marked proteinuria and increased urinary red cell excretion. Idiopathic retroperitoneal fibrosis can also result in the formation of perivesical varices secondary to caval compression (Kratz, 1983) and severe haematuria has been reported in a patient with portal hypertension who developed venous collaterals around the bladder connecting the mesenteric and body wall veins (Sano *et al.*, 1989).

One of our patients with vena caval obstruction and venous collateral formation had X-ray appearances typical of pelvic lipomatosis on IVU, although on CT no areas were seen of increased lucency compatible with fat deposition in the pelvis. It has been reported that venous varicosities and pelvic lipomatosis can coexist (Abbott and Skinner, 1974; Schechter, 1974) but it is uncertain which of these rare conditions is the primary abnormality.

Previous venous thrombosis is not uncommon in men undergoing prostatectomy and the incidence of collateral veins of the type described here is unknown in this population. On present evidence it seems unlikely that they often cause serious venous bleeding in this situation. On the other hand, the management of patients who present with spontaneous haematuria would be difficult if continuing bleeding made treatment necessary. It might be possible to treat gross haematuria by means of interventional radiological techniques, including the use of coils or other agents designed to produce thrombosis, although it seems likely that further collateral formation would occur.

## Acknowledgements

We thank Messrs W. K. Yeates, R. R. Hall and P. D. Ramsden for permission to report these patients.

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# Measurement of Voiding Pressures on Ambulatory Monitoring: Comparison with Conventional Cystometry

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Summary—A series of 20 patients underwent conventional medium fill cystometry (CMG) and ambulatory monitoring during natural bladder filling (AM). The measurement of voiding pressures by the 2 techniques was compared.

The maximum subtracted detrusor contraction pressure recorded during CMG (50 ± 30 cm $H_2O$) was significantly less than that recorded during AM (86 ± 35 cm $H_2O$). Voiding pressures during natural filling are greater than those observed during conventional urodynamic studies: this finding may have important implications in the definition of bladder outflow obstruction.

The usual method of investigating bladder function involves filling the bladder with fluid at rates of 20 to 100 ml/min whilst bladder and rectal pressures are measured (CMG). When the bladder is full the patient voids and the urine flow rate is recorded. Such investigations are quick and convenient to perform and give useful clinical information, although the question remains open as to whether the behaviour of the bladder is similar to that found during natural filling.

Over the past few years we have been using a system of ambulatory monitoring of bladder and detrusor pressures which allows study of the behaviour of the bladder during natural filling (AM) (Griffiths *et al.*, 1987, 1989).

In men with chronic retention and in patients with low bladder compliance caused by neuropathic dysfunction we have observed marked differences between ambulatory monitoring during natural bladder filling and conventional urodynamics, particularly in the magnitude of the pressure rise during filling and in the incidence of phasic detrusor activity (Styles *et al.*, 1988; Webb *et al.*, 1989). During the course of these and other studies we gained the impression that detrusor pressure during voiding was greater during AM than during CMG. A retrospective study was therefore performed to compare voiding pressures recorded by the 2 techniques in the same patients.

## Patients and Methods

We reviewed 20 patients (13 female and 7 male, mean age 43 ± 25 years). Each patient was investigated by both ambulatory monitoring and conventional cystometry. Patients with chronic retention or neuropathic bladder dysfunction were excluded, as were those in whom voluntary voiding could not be distinguished from incontinence occurring as a result of detrusor instability during CMG. Ambulatory monitoring studies were performed because of suspected detrusor instability: 8 patients had detrusor activity on CMG which failed to meet International Continence Society criteria for instability and 12 had no demonstrable detrusor instability.

CMG was performed as follows. Bladder and rectal pressures were measured by means of 4F fluid filled lines connected to external transducers which were zeroed at the level of the symphysis pubis and the bladder was filled at 100 ml/min via a 10F urethral catheter. The ambulatory monitoring system used microtip transducers mounted on 6F catheters to measure intravesical and rectal pres-

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

sures which were recorded in a solid state memory which had a capacity of 6 h. This method has been reported elsewhere in greater detail (Griffiths *et al.*, 1989). Results were analysed using tests appropriate for paired, non-parametric data.

## Results

Bladder and detrusor pressures were recorded on the basis of a single voiding cycle during CMG but on the basis of an average of 3 voids during AM.

Resting detrusor pressure measured by the 2 techniques was similar (CMG $= 1.5 \pm 2$ cm $H_2O$; AM $= 0.75 \pm 5$ cm $H_2O$; $P = \mathrm{NS}$), but end filling pressure during CMG ($5.7 \pm 5.4$ cm $H_2O$) was significantly greater than during AM ($1.2 \pm 5$ cm $H_2O$; $Z = -2.1$; $P < 0.05$, Wilcoxon test). The voided volumes measured during AM and CMG did not differ significantly (CMG $225 \pm 128$ ml; AM $188 \pm 93$ ml; $Z = -1.9$; $P = 0.07$, Wilcoxon test).

Subtracted detrusor contraction pressure recorded on CMG ($50 \pm 30$ cm $H_2O$) was significantly smaller than that recorded during AM ($86 \pm 35$ cm $H_2O$; $Z = -3.09$; $P < 0.002$) (Fig. 1). We also measured bladder voiding pressure; a derived measurement was used which took into account the different magnitudes of pressure rise during filling: this was a combination of bladder pressure rise during filling plus bladder contraction pressure. This combined voiding pressure during CMG ($55 \pm 32$ cm $H_2O$) was also significantly smaller than during AM ($87 \pm 34$ cm $H_2O$; $Z = -2.89$; $P < 0.002$) (Fig. 2).

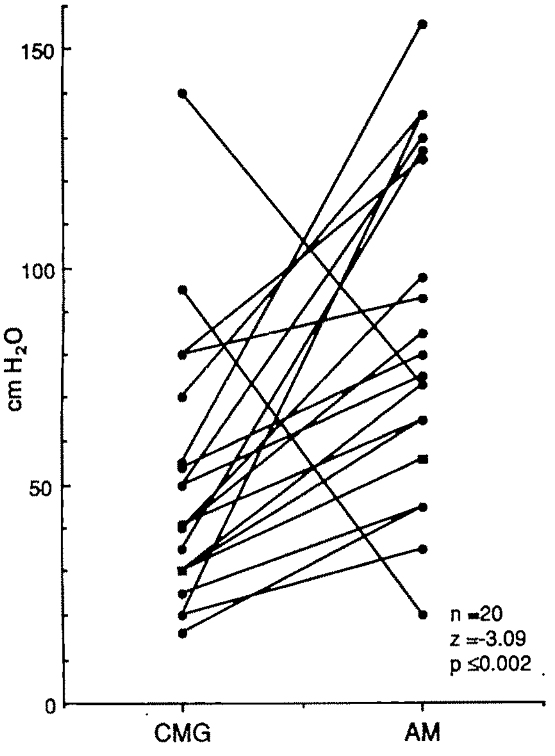

**Fig. 1** Comparison of subtracted detrusor contraction pressures during CMG and AM.

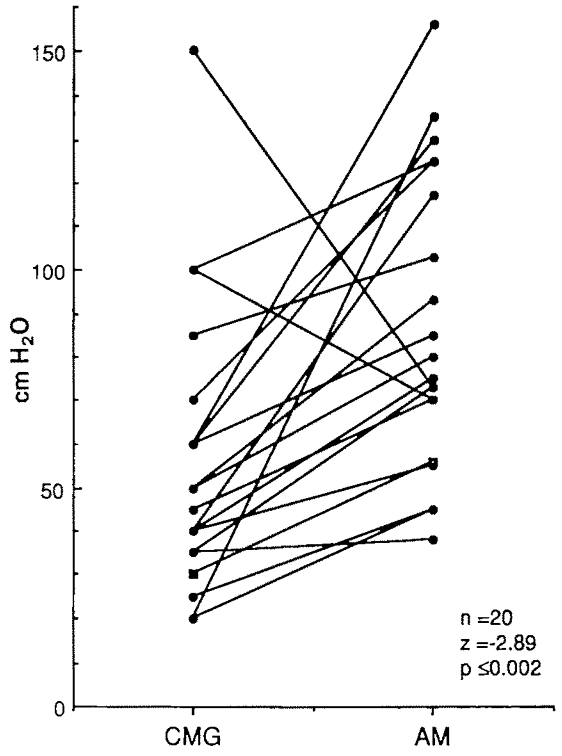

**Fig. 2** Comparison of bladder voiding pressure measured during CMG and AM. This pressure was equal to the bladder pressure rise during filling plus the bladder contraction pressure.

## Discussion

This study supported our impression that the voiding pressures recorded during AM were significantly greater than those recorded during CMG in the same patients. The reason for this is not clear, but it may be that bladder contraction is impaired following artificial filling in excess of normal physiological rates. Various differences between the 2 techniques are listed in the Table. In both techniques the transducers and recorders were calibrated prior to each study and recorded accurately within the physiological pressure range. The

**Table** Potential Differences between the Techniques of AM and CMG

| | *AM* | *CMG* |
|---|---|---|
| Fluid | | |
| Composition | Urine | Contrast medium |
| Temperature | 37°C | Room temperature |
| Filling | | |
| Rate | Physiological | 100 ml/min |
| Route | Ureteric | *per urethram* |
| Equipment | | |
| Transducers | Catheter tip | External |
| Recorders | Digital | Analogue |
| Environment | Ward | CMG laboratory |

mean base-line drift measured by the solid state transducers during a study averaged 2 cm $H_2O$ (range $-4$ to $+4$ cm $H_2O$). Such drift could not have accounted for the observed differences in detrusor contraction pressure. Another difference was the type and size of catheters. Those used during CMG were slightly larger than those used during AM but the results of a previous study suggest that this factor would, if anything, have resulted in slightly higher voiding pressures during CMG (Neal *et al.*, 1987).

It is unlikely that the small and statistically insignificant difference in voiding volume found between the 2 techniques would lead to marked differences in voiding pressure. The most likely cause of the difference in the behaviour of the bladder during voiding is the different method of filling the bladder. One method uses urine at body temperature passing through the ureter at physiological rates; the other uses contrast medium or saline at room temperature via a urethral catheter at rates consistently in excess of maximum renal output.

This retrospective study suggests that there may be differences in voiding pressures measured during natural filling and conventional urodynamic studies. A prospective study is now required to investigate the possible causes of these differences.

## Acknowledgements

We thank Messrs Essenhigh, Hall and Powell for permission to study their patients.

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# Voiding Patterns in Men Evaluated by a Questionnaire Survey

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Summary—A questionnaire on obstructive and irritative voiding symptoms was sent to 572 men aged between 20 and 79 years, selected at random from the National Register; 337 questionnaires were completed. None of the responders had consulted a doctor because of voiding symptoms. There was a significant increase in voiding symptoms and in the obstructive, irritative and total symptom scores between the fifth and sixth decades, whereas the increases in the other decades were small. Only the prevalence of terminal dribbling was uniform. The prevalence of single obstructive and irritative voiding symptoms in men aged 60 to 79 years without subjective prostatism was the same as in patients admitted with prostatism, although most of the men had milder symptoms. Only nocturia and urge incontinence were more prevalent in patients admitted with prostatism. About 20% of men in the oldest decades had symptoms equal in severity to those found in men undergoing prostatectomy; 29% and 11% of men in the seventh decade had nocturia twice and 3 times or more respectively; 19% complained of urge incontinence. More information on possible treatment is needed.

Voiding symptoms are common in patients with diseases of the lower urinary tract, but voiding patterns in men with subjectively satisfactory micturition have seldom been investigated.

Certain urodynamic measurements are mandatory in the pre-operative evaluation of patients with prostatism (Abrams, 1977; Abrams *et al.*, 1979; Blaivas, 1983; Siroky and Krane, 1983). The uroflowmetry variables have been found to correlate poorly with symptom scores and single symptoms (Castro *et al.*, 1969; Abrams, 1977; Abrams and Feneley, 1978; Andersen, 1982; Brooks *et al.*, 1983; Siroky and Krane, 1983; Nielsen *et al.*, 1986). Furthermore, the results of uroflowmetry and pressure-flow measurements have been found to overlap in patients with prostatism and in age-matched males without voiding symptoms (Andersen *et al.*, 1978; Jensen *et al.*, 1986). Blind trials have shown that neither uroflowmetry nor pressure-flow measurements can predict which patients will benefit from surgery for benign prostatic hypertrophy (Jensen *et al.*, 1983, 1986; Dørflinger *et al.*, 1986). When assessing patients with prostatism some authors advocate the analysis of voiding symptoms only, regarding routine urodynamic tests as unnecessary (Frimodt-Møller *et al.*, 1984). Thus various scoring systems have been developed to classify the severity of symptoms in patients with prostatism (Madsen and Iversen, 1983; Jensen *et al.*, 1986; Nielsen *et al.*, 1986). The aim of this study was to assess the prevalence of voiding symptoms and to calculate symptom scores in randomly selected men aged between 20 and 79 years who had not consulted a doctor for voiding symptoms.

## Patients and Methods

A detailed questionnaire on obstructive and irritative voiding symptoms, previous abdominal and urinary tract surgery, present drug treatment, past and present diseases relating to the bladder, and urethral function was sent to 572 men in the metropolitan population. They were selected randomly from the National Register.

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**Table 1** Symptom Scores

| | *Points* | | | | |
|---|---|---|---|---|---|
| *Symptoms* | *0* | *1* | *2* | *3* | *4* |
| Hesitancy | None | | Yes | | |
| Intermittency | None | | Yes | | |
| Stream | Normal | Variable | | Weak | Dribbling |
| Terminal dribbling | None | | Yes | | |
| Diurnal frequency (h) | >3 | 2–3 | 1–2 | <1 | |
| Nocturia | 0–1 | | 2 | 3–4 | >4 |
| Urge (incontinence) | None | Now and then, ÷ incontinence | Now and then, + incontinence | Often or always, + incontinence | |

Obstructive symptoms comprised hesitancy, intermittency, decreased stream and terminal dribbling; irritative symptoms comprised urge incontinence, diurnal frequency and nocturia. These symptoms were scored according to a numerical system (Jensen *et al.*, 1986) (Table 1) and obstructive, irritative and total scores were calculated. The maximum obtainable score for both obstructive and irritative symptoms was 10 points, *i.e.* the 2 categories were considered equally important.

The questionnaires were returned by 382 men (67%) (Table 2). Of these, 14 questionnaires were unanswered and 18 were only partly completed; 11 men had had a prostatectomy and 2 had been treated for a urethral stricture. Accordingly, the symptoms in 337 men (59%) were registered in the symptom score scheme. The questionnaires from 368 men (64%) were used in the descriptive prevalence studies. Only the 14 unanswered questionnaires were omitted. Since 18 were only partly completed, the number of men appearing in the results is variable.

The Kruskall-Wallis analysis of variance and the Mann-Whitney rank sum test was used for statistical calculations. $P<0.05$ was considered statistically significant.

**Table 2** Percentage of Questionnaires Returned

| *Decades* | *Percentage* |
|---|---|
| Second | 55 |
| Third | 54 |
| Fourth | 64 |
| Fifth | 69 |
| Sixth | 76 |
| Seventh | 87 |
| Overall (n = 382) | 67 |

## Results

A total of 67 men (19%) complained of hesitancy (Fig. 1A) but this was a persistent symptom in only 4 (1.1%); 70 men (20%) complained of intermittency (Fig. 1B) but in most cases this was fluctuating and inconsistent; 121 men (34%) claimed to have a weak stream but in only 4% was it permanent (Fig. 1C). The prevalence of hesitancy, intermittency and weak stream increased between the second and the seventh decades, with the greatest increase between the fifth and sixth decades.

Terminal dribbling was reported by 179 men (51%) (Fig. 1D). In 37% it was present to a slight degree but in 14% it was a greater problem. Unlike the other obstructive symptoms, this symptom was evenly distributed amongst all age groups.

Diurnal frequency <3 h was reported by 177 men (50%) (Fig. 2A), mainly in the sixth and seventh decades. The severity of this symptom increased in these decades.

Nocturia was a problem in 56 men (16%) (Fig. 2B) and urgency in 139 (38%) (Fig. 2C). Overall, 35 men (10%) complained of urge incontinence and almost 20% in the seventh decade had urge incontinence. The prevalence of nocturia, urgency and urge incontinence increased throughout the decades.

Table 3 shows the obstructive, irritative and total symptom scores. Statistically significant increases were found in both obstructive, irritative and total symptom scores from the fifth to the sixth decades. In earlier decades the changes in score were not statistically significant.

In the fourth, fifth, sixth and seventh decades 2, 7, 18 and 23% of men respectively had total symptom scores >9, which is the median value in patients with subjective prostatism (Jensen *et al.*, 1986).

Drugs with a possible influence on micturition such as $\alpha$- and $\beta$-blocking agents, diuretics, anti-

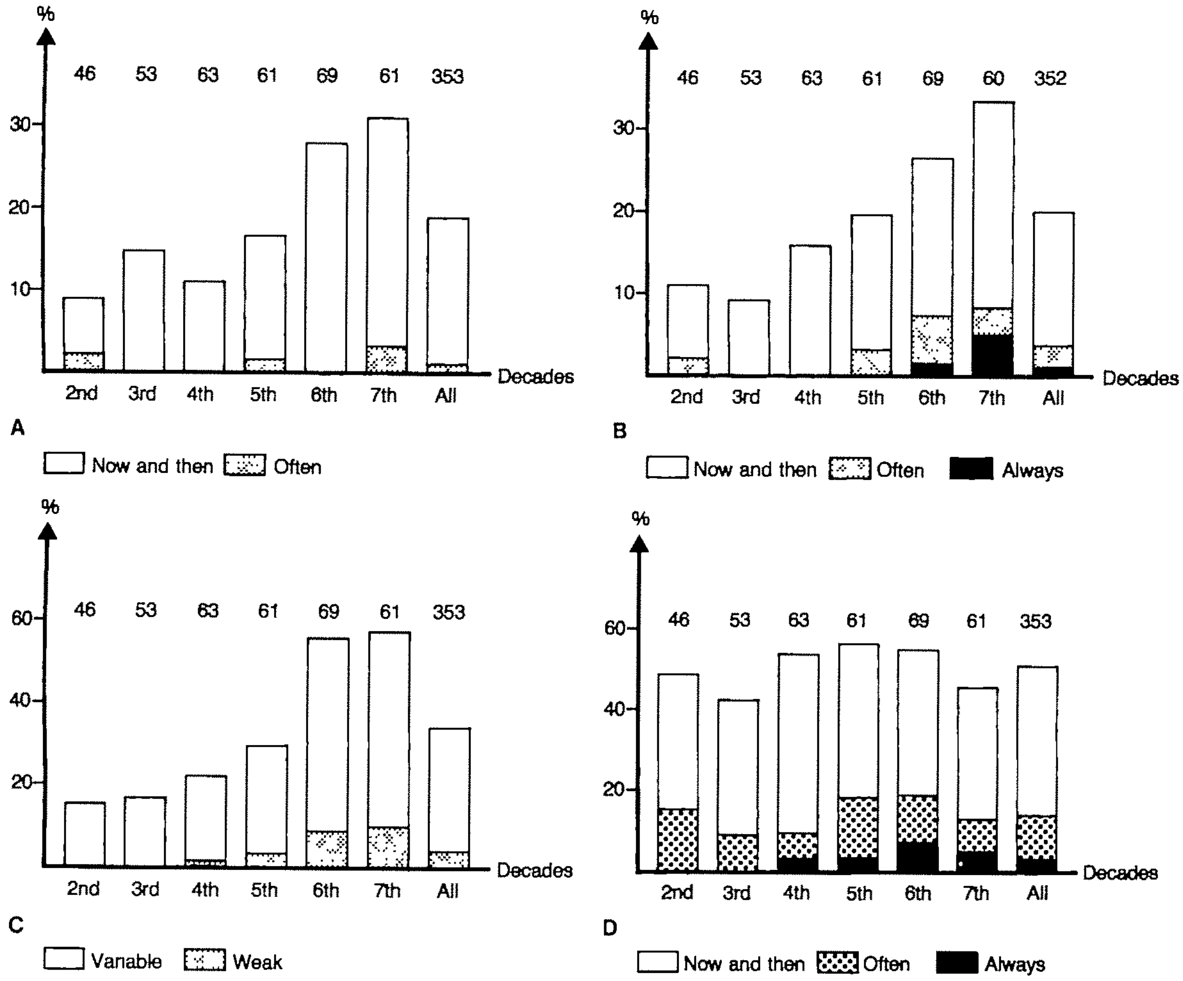

**Fig. 1** (A) Hesitancy. (B) Intermittency. (C) Stream. (D) Terminal dribbling.

depressants and neuroleptics, were used by 24% of men in the seventh decade, 17% in the sixth decade, 7% in the fifth, 3% in the fourth, 2% in the third and none in the second decade.

**Table 3** Obstructive, Irritative and Total Symptom Scores (median, range)

| | *Decades* | | | | | |
|---|---|---|---|---|---|---|
| *Scores* | *Second* | *Third* | *Fourth* | *Fifth* | *Sixth* | *Seventh* |
| Obstructive | 1.5<br>(0–6) | 2.0<br>(0–7) | 2.0<br>(0–7) | 2.0<br>(0–7) | 2.0<br>(0–9) | 3.0<br>(0–9) |
| Irritative | 1.0<br>(0–3) | 1.0<br>(0–5) | 0.0<br>(0–5) | 1.0<br>(0–5) | 2.0<br>(0–8) | 2.0<br>(0–7) |
| Total | 2.0<br>(0–7) | 2.0<br>(0–7) | 2.0<br>(0–10) | 2.0<br>(0–10) | 4.0<br>(0–17) | 5.5<br>(0–16) |

## Discussion

The prevalence and severity of voiding symptoms increased between the second and seventh decades, with a marked increase in prevalence between the fifth and sixth decades. This increase is probably caused by infravesical obstruction due to benign prostatic hypertrophy, but it is not known whether the increase in both prevalence and severity is the result of increasing age or more pronounced infravesical obstruction.

Only terminal dribbling was uniformly prevalent. This probably reflects a different interpretation of the symptom by the various age groups.

The frequency of the other symptoms of prostatism and the calculated symptom scores agree with the findings of Jensen *et al.* (1986) (Table 4). The differences between the 2 studies probably reflect

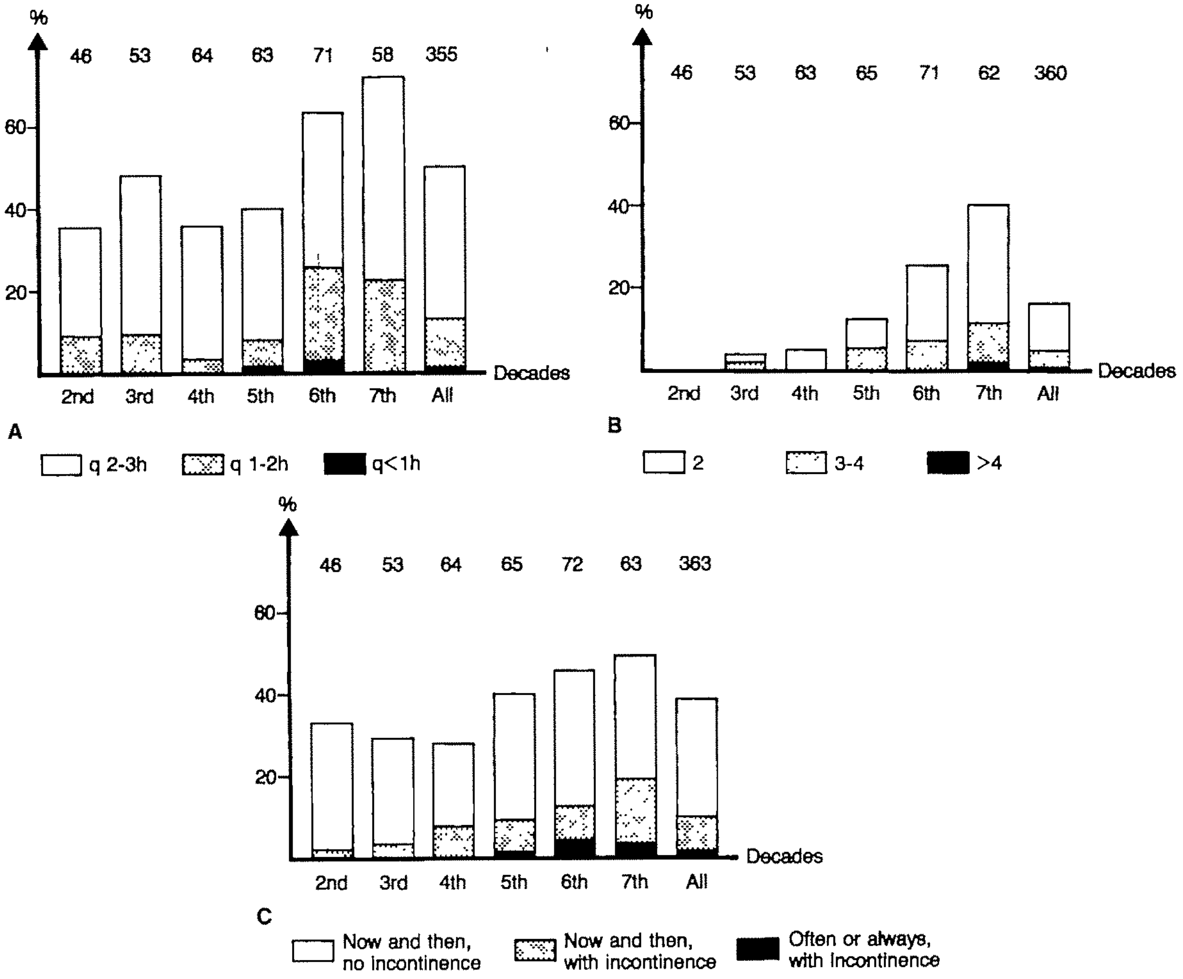

**Fig. 2** (A) Diurnal frequency. (B) Nocturia. (C) Urge incontinence.

**Table 4** Prevalence of Voiding Symptoms in Fifth to Seventh Decades Compared with Study by Jensen *et al.* (1986)

| | *Decades* | | | | | |
|---|---|---|---|---|---|---|
| | *Fifth* | | *Sixth* | | *Seventh* | |
| *Symptoms* | *A** *(n=39)* | *B†* *(n=61)* | *A** *(n=39)* | *B†* *(n=69)* | *A** *(n=29)* | *B†* *(n=61)* |
| Hesitancy | 13 | 17 | 23 | 28 | 21 | 31 |
| Intermittency | 18 | 20 | 39 | 27 | 38 | 33 |
| Weak stream | 31 | 30 | 56 | 56 | 62 | 57 |
| Terminal dribbling | 39 | 56 | 51 | 55 | 45 | 46 |
| Diuria | 54 | 40 | 54 | 63 | 59 | 72 |
| Nocturia | 8 | 12 | 33 | 25 | 45 | 40 |
| Urgency | 41 | 40 | 41 | 46 | 48 | 49 |

* A = Jensen *et al* (1986).
† B = Present study.

**Table 5** Prevalence of Voiding Symptoms in Patients with Subjective Prostatism compared with Men in Fifth to Seventh Decades in the Present Study. (Numbers indicate Percentages)

| *Symptoms* | *Prostatism** | *Fifth decade* | *Sixth–seventh decades†* |
|---|---|---|---|
| Hesitancy | 29–78 | 17 | 30 |
| Intermittency | 29 | 20 | 30 |
| Weak stream | 46–85 | 30 | 57 |
| Terminal dribbling | 68 | 56 | 51 |
| Diuria | 38–85 | 40 | 68 |
| Nocturia | 40–85 | 12 | 33 |
| Urgency | 32–68 | 40 | 48 |
| Urge incontinence | 16–30 | 9 | 16 |

* Based on findings in other studies.
† Mean values from sixth and seventh decades.

the fact that ours was based on a questionnaire survey and the other on interviews.

Table 5 compares the prevalence of symptoms between patients with subjective prostatism (Craigen *et al.*, 1969; Abrams, 1977; Abrams and Feneley, 1978; Abrams *et al.*, 1979; Andersen, 1982; Neal *et al.*, 1987; Simonsen *et al.*, 1987) and men in the fifth to seventh decades without subjective prostatism. The wide range of figures for patients with prostatism is explained by different definitions of the symptoms. However, a great deal of overlap exists between men aged 60 to 79 years without subjective prostatism and patients complaining of prostatism. Only nocturia and urge incontinence are more prevalent in patients with prostatism. This agrees with the assumption that such patients consider the irritative symptoms to be at least as annoying as the obstructive ones (Jensen *et al.*, 1986).

Although there is considerable overlap in the single symptoms, the calculated obstructive, irritative and total symptom scores are significantly higher in patients with prostatism than in age-matched men without prostatism (Jensen *et al.*, 1986). In the present study we found a statistically significant increase in both obstructive, irritative and total symptom scores in the fifth and sixth decades, whereas the increases in the other decades were not statistically significant. A median total score of 9 (range 3–16) was reported in patients with subjective prostatism (Jensen *et al.*, 1986). In the present study 2, 7, 18 and 23% of men in the fourth, fifth, sixth and seventh decades respectively had total scores of 9 or more. Thus 20% of men in the oldest decades without subjective prostatism had symptoms equal in severity to those in men undergoing prostatectomy. However, Frimodt-Møller *et al.* (1984) and Jensen *et al.* (1988) reported median total symptom scores >9, but only the latter workers used the same scoring system as we did.

It was surprising that so many men in the two oldest age groups had so many severe voiding symptoms without consulting their doctor. In the seventh decade, 29% had nocturia twice, 11% had nocturia 3 times or more, and 19% complained of varying degrees of urge incontinence. Many might be helped by prostatic surgery, anticholinergic drugs, changes or dose changes of drugs such as diuretics, α- and β-blocking agents, neuroleptics, etc, or changes in drinking habits. More information on the treatment of these voiding symptoms is needed.

Although there is a certain amount of overlap in symptom scores, especially in the prevalence of single voiding symptoms, between men with and without subjective prostatism, it is possible to classify the severity of prostatism by calculating the symptom scores. These scores alone can probably not be used as an indication for treatment, since it is reported that only 75% of patients referred for prostatism do in fact have infravesical obstruction due to benign prostatic hypertrophy (Abrams and Feneley, 1978; Andersen, 1982; Simonsen *et al.*, 1987).

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# Assessment of the Poorly Contractile or Acontractile Bladder in the Older Male in the Absence of Neuropathy

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Summary—Up to 30% of patients who undergo prostatectomy are left with residual symptoms. Most have persistent detrusor instability, but some have poorly contractile or acontractile bladders. Over a 2-year period, 42 neurologically normal patients were shown to have a hypocontractile or acontractile bladder on urodynamic testing; 27 had undergone outflow tract surgery. Four patients who were totally incontinent had undergone at least 2 transurethral resections. The remainder had severe frequency, urgency and nocturia. Urodynamically, all but 7 patients with poor compliance had normal filling cystometrograms, all but 8 had residual urine volumes less than 100 ml, and 26 had less than 5 ml. Thus their symptoms are difficult to explain. Apart from the insertion of an artificial sphincter in those with total incontinence, treatment did not improve any of these patients.

Up to 30% of patients continue to have symptoms after prostatectomy. These usually consist of persistent frequency, nocturia and urgency, even urge incontinence, and are usually a result of persistent detrusor instability (Rollema and Van Mastrigt, 1987). However, a smaller group with urge syndrome after TURP, and some younger patients with similar symptoms without surgery, prove to have poorly contractile or acontractile bladders and a poor flow rate. The identification of these "low flow/low pressure" groups prompted an assessment of the management and treatment of these patients.

## Patients and Methods

Over a 2-year period, 86 patients aged 44 to 80 years with the urge syndrome underwent urodynamic assessment and were shown to have poorly contractile or acontractile bladders. Forty-four were excluded from the series because their disturbance of bladder function was considered to be secondary to neuropathy; 42 were neurologically normal. Most of the older patients had undergone outflow tract surgery (Table 1) but 17 in the younger age group (all under 55 years and all but 4 under 50 years) had not.

Four patients presented with total incontinence following multiple TURPs. The remainder all had severe urge syndrome, though perineal pain was a notable feature in a few (Table 2).

Urodynamic assessment of the patients is shown in Table 3. Somewhat arbitrarily, patients were considered to fall into the "low flow/low pressure"

**Table 1** Previous Surgery

| | |
|---|---|
| TUR × 1 | 15 |
| Bladder neck incision | 3 |
| TUR × 2–5 | 7 |
| None | 17 |

**Table 2** Symptoms

| | |
|---|---|
| Frequency, nocturia, urgency (FNU) | 33 |
| FNU + loin pain | 1 |
| FNU + perineal pain | 4 |
| Incontinence (after TUR × 2–5) | 4 |

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**Table 3** Urodynamic assessment

| | | |
|---|---|---|
| Filling CMG | Normal | 35 |
| | Poor compliance | 7 |
| Voiding pressure (Cm $H_2O$) | O (straining only) | 27 |
| | 10–30 | 15 |
| Flow rate | 10 or less | 28 |
| | 10–15 | 14 |
| Residual urine | <5 | 26 |
| | 5–10 | 8 |
| | 100–400 | 8 |

category if their voiding detrusor pressure was less than 30 cm $H_2O$ and their flow less than 15 ml/s (Fig. 1). The majority, however, voided entirely by straining, had flow rates <10 ml/s and yet had residual urine volumes <10 ml and usually emptied to completion. Most patients had normal filling cystometrograms, although a few demonstrated poor compliance (Fig. 2).

Several treatments were instituted in an attempt either to improve detrusor contractility with long-acting cholinergic compounds or to improve outflow at bladder neck level by bladder neck incision in those not previously operated on, or by alpha adrenergic blockade (Stephenson, 1986). Patients with total incontinence following multiple TURs were treated by the insertion of an artificial urinary sphincter.

**Table 4** Results

| *Subsequent treatment* | | *Improved/cured* |
|---|---|---|
| Ubretid/carbachol | (16) | 1 |
| Prazosin | (14) | 0 |
| Bladder neck incision | (4) | 0 |
| AMS 800 sphincters | (4) | 4 |

## Results

The results of the various treatments were characterised by a complete lack of success apart from the small group rendered incontinent, who were all cured by the artificial urinary sphincter; these patients did not subsequently develop the urge syndrome (Table 4). One patient (not in this series) has improved considerably on imipramine, and in the face of such a hopeless response to other treatment, perhaps even such anecdotal success is worth pursuing. Otherwise it is our current policy to advise these patients to live with their symptoms and to discharge them, even though many are severely disabled and very unhappy.

## Discussion

Previous studies on patients failing to void, or voiding by abdominal straining, suggest that poorly

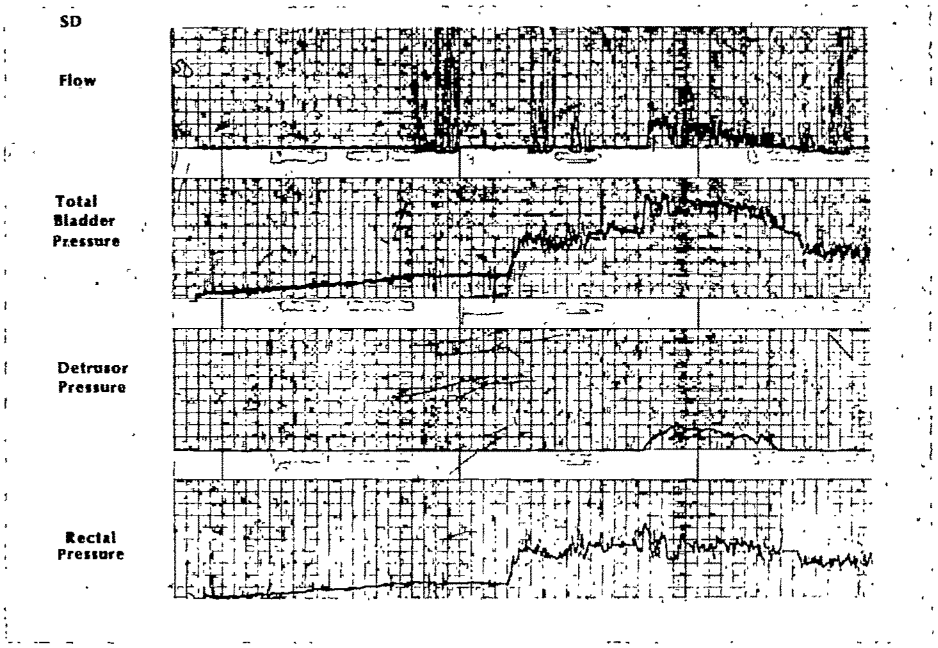

**Fig. 1** Urodynamic tracing demonstrating a low flow (10 ml/s) low pressure (20 cm $H_2O$) voiding pattern.

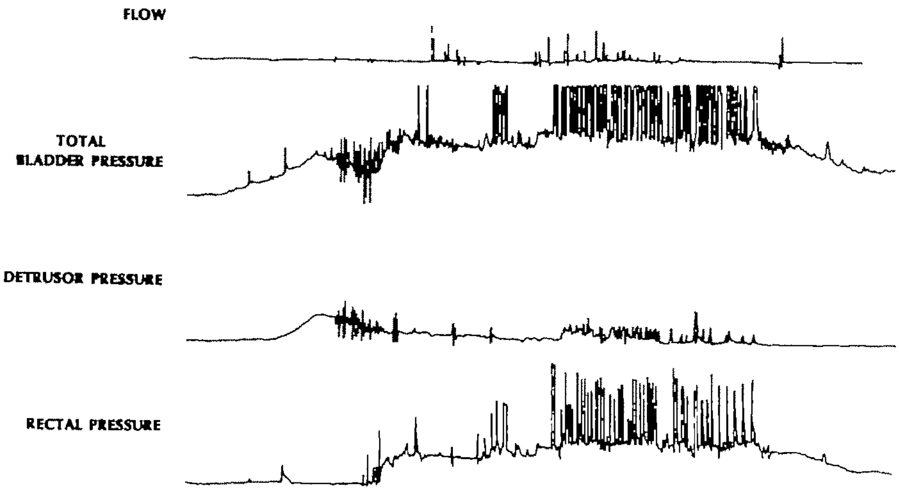

**Fig. 2** Poor compliance demonstrated on filling. No detrusor pressure generated on voiding (straining only).

contractile or acontractile bladders referred for urodynamic assessment are caused by an overt neurological defect in approximately half and to idiopathic detrusor failure in the other half (Kirby *et al.*, 1983).

Without full urodynamic assessment it is not possible to exclude outflow obstruction and poor flow rate, and as a consequence many patients in the older age group undergo prostatectomy (and regrettably, in some cases, repeat procedures). The demand on urodynamic facilities makes it impractical and in most cases unnecessary to perform cystometry on all men with symptoms of outflow obstruction except in the younger are group. However, persistence of the urge syndrome after TURP is an absolute indication for video urodynamic assessment to identify whether persistent instability, residual obstruction, or a poorly functioning detrusor is the cause.

It remains unclear why patients with poor detrusor function have frequency, nocturia and urgency, except for the few with poor compliance and those who fail to empty completely. In the majority there must be a sensory cause for their symptoms. What is clear is that none of the treatments has made the slightest difference to their symptoms, other than the use of an artificial urinary sphincter in those rendered inappropriately incontinent. Treatment should be directed towards eradicating the presumed sensory urgency rather than trying to improve detrusor tone.

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# Surgical Management of the Congenital Neuropathic Bladder

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Summary—We have previously described 3 types of lower urinary tract dysfunction in the congenital neuropathic bladder—contractile, intermediate and acontractile—accounting for 35, 40 and 25% of patients respectively. Subsequent urodynamic and surgical experience has shown that the intermediate type is commoner and the acontractile type less common than was thought. The contractile group accounts for 31% of patients and rarely requires surgery (a "clam" ileocystoplasty). The acontractile group accounts for only 9% but more commonly requires surgical treatment, usually the implantation of an artificial urinary sphincter (AUS). The intermediate group accounts for 60% of patients and usually requires surgery. If there is no significant sphincter weakness incontinence, a "clam" ileocystoplasty alone is performed; if there is sphincter weakness, a "clam and a cuff" procedure is performed with implantation of the remainder of the AUS at a later date, if required.

Most patients with lower urinary tract dysfunction as a result of congenital neuropathy do not require surgical intervention because it can be controlled satisfactorily by other means (Mundy and Stephenson, 1984). When surgery is required it is usually palliative, since most patients are unsuitable for specific corrective surgical treatment because of their poor general condition or other circumstance.

In patients who are selected for specific corrective surgical treatment of their lower urinary tract dysfunction, pre-operative videourodynamic studies are mandatory. Mundy *et al.* (1985) reported 3 distinct types of lower urinary tract dysfunction in congenital neuropathy—contractile, intermediate and acontractile. These findings were almost identical to those of Rickwood *et al.* (1982) and based on their terminology. The most striking difference between these 3 types, but not necessarily the most important, was the pattern of detrusor activity. In the contractile group, detrusor activity was of sufficient amplitude and duration to give a useful degree of bladder emptying, assuming that any associated bladder outflow obstruction was eliminated. In the intermediate group, detrusor activity was present but was of insufficient amplitude and duration to give a useful degree of bladder emptying irrespective of any outflow obstruction. In the acontractile group there was no significant detrusor activity. We reported that the 3 groups accounted for 35, 40 and 25% of patients respectively.

Patients with acontractile dysfunction and significant sphincter weakness incontinence who were thought suitable for surgical treatment were treated by the implantation of an artificial urinary sphincter. We subsequently found that the bladder of more than half of the patients treated in this way changed progressively from a low pressure type to a high pressure type in the face of increased sphincteric resistance produced by the AUS. The reason for this was that although we had followed the terminological recommendations of the International Continence Society at that time, our previous urodynamic interpretation had been lax and we had included in the acontractile group patients who had detrusor pressure waves of low amplitude that we had thought were insignificant.

As a result of this experience we have been stricter in our urodynamic assessment and have paid greater attention to detrusor dysfunction in patients selected for surgical treatment.

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## Patients and Methods

The urodynamic findings in 214 patients referred with congenital neuropathic lower urinary tract dysfunction are shown in Table 1. The intermediate type of dysfunction was more common and the acontractile type less common than previously thought.

Of the 214 patients, 85 were selected for specific surgical treatment. The numbers and percentages selected and the operations performed are shown in Table 2, and the reasons why patients were not selected for surgical treatment in Table 3. The commonest reasons for non-selection were that the incontinence was controlled satisfactorily by other means or that the patient's general neurological condition made such treatment unrealistic.

In the contractile group the majority of patients were controlled with oxybutynin; when this failed and surgery was indicated, a "clam" ileocystoplasty (Mundy, 1988) was performed. In the acontractile group when surgery was indicated an artificial urinary sphincter was implanted.

In the intermediate group a few patients underwent implantation of an AUS alone but most underwent a "clam" ileocystoplasty with or without simultaneous implantation of an AUS cuff. If there was no significant sphincter weakness incontinence (SWI), a cystoplasty alone was performed. If there was significant SWI, an AUS cuff was implanted at the same time as the "clam" ileocystoplasty (a "clam and a cuff" procedure). The question of significant SWI was decided on the basis of the "leak pressure", that is the detrusor pressure at which incontinence occurred during urodynamic evaluation, and the residual urine volume. If there was a substantial residual urine volume in the face of a detrusor pressure $>25$ cm $H_2O$, there was deemed to be no significant SWI. If there was little or no residual urine irrespective of detrusor pressure, significant SWI was assumed to be present.

**Table 1** Types of Neuropathic Bladder Dysfunction

| *Type* | *1985 percentages** | *1989 percentages* |
|---|---|---|
| Contractile | 35 | 31 |
| Intermediate | 40 | 60 |
| Acontractile | 25 | 9 |

* From Mundy *et al.* (1985).

The rationale of the "clam and a cuff" approach rather than simultaneous implantation of the whole of an AUS, or alternatively to wait and see if an AUS proved necessary, is discussed below. It is because it has been our experience that it is not possible to be sure (in most patients) whether apparently significant SWI on pre-operative urodynamic assessment will still be significant after a cystoplasty, whereas it is much easier to implant the cuff at the time of the cystoplasty than it is at a later date after a cystoplasty. Indeed the presence of a cuff alone has been found to correct SWI in a significant percentage of patients, making the rest of the device unnecessary.

It is emphasised that this was a highly selected group of patients, and in an unselected group of patients with congenital neuropathic lower urinary tract dysfunction the number treated surgically would be lower, although the percentages treated by the different surgical modalities within each type would probably be much the same. Furthermore, these figures refer only to patients who had had no previous surgical intervention and would be different if those who had previously had bladder neck incisions, external sphincterotomies or other surgical manoeuvres were included.

It was previously our practice to perform a routine sphincterotomy before implantation of an AUS in order to achieve complete bladder emptying but in recent years routine sphincterotomy has been abandoned in favour of clean intermittent self-catheterisation (CISC) to achieve this goal.

**Table 2** Surgery for the Congenital neuropathic Bladder According to the Type of Dysfunction (in Patients who have had no Previous Lower Urinary Tract Surgery)

| *Type* | *No. of patients** | *Selected for specific treatment* | *(%)* | *Cystoplasty alone* | *AUS alone* | *Cystoplasty plus AUS†* |
|---|---|---|---|---|---|---|
| Contractile | 66 | 8 | (12) | 8 | — | — |
| Intermediate | 127 | 65 | (51) | 19 (29%) | 4 (6%) | 42 (65%) |
| Acontractile | 21 | 12 | (57) | — | 12 | — |

* A highly selected group often referred specifically for surgery.
† The "clam and cuff" in the first instance with implantation of the remainder of the AUS at a later date if necessary.

**Table 3** Reasons for Not Selecting Patients for Specific Corrective Surgical Treatment

Incontinence controlled satisfactorily by other means
Inadequately motivated
Immobility
Severe deformity
Lack of manipulative skills (for CISC or to use an AUS)
Insufficient intelligence
Severe emotional disorder
Too young

All of these are relative contraindications and the patients' individual circumstances often affected the final decision.

## Results

The urodynamic findings are shown in Table 1 and the results of treatment in Table 4. All 8 patients treated by "clam" ileocystoplasty alone in the contractile group had a satisfactory result, as did the 12 treated by implantation of an artificial urinary sphincter in the acontractile group, although some patients in the latter group had AUS-related complications requiring revision before that satisfactory result was achieved.

Of the 19 patients in the intermediate group who were thought to have little or no sphincter weakness incontinence, 2 (10%) subsequently required implantation of an AUS for this reason. Of the 42 treated by a "clam" ileocystoplasty with simultaneous implantation of an AUS cuff (a "clam and a cuff"), 18 (43%) required implantation of the remainder of the AUS components at a later date to achieve continence. The other 24 (57%) were either completely continent or were sufficiently satisfied with their urinary control not to want further surgical intervention.

**Table 4** Congenital Neuropathic Bladder—Results of Surgical Treatment

| *Type* | *Procedure* | *No. of patients* | *Results* |
|---|---|---|---|
| Contractile | Clam alone | 8 | All continent |
| Intermediate | Clam alone | 19 | 17 continent<br>2 subsequently required an AUS |
| | "Clam and a cuff" | 42 | 24 continent<br>18 required remainder of AUS |
| | AUS alone | 4 | All continent |
| Acontractile | AUS alone | 12 | All continent |

## Discussion

There have been 3 main changes in our approach to patients with congenital neuropathic lower urinary tract dysfunction. Firstly, we have been stricter in our urodynamic interpretation and have found the intermediate type of dysfunction is much commoner than the contractile or acontractile types, and much more likely to require surgical intervention. As a result, we have learned to pay more attention to detrusor dysfunction and we believe that except in extreme forms of sphincter weakness incontinence, detrusor dysfunction is more important than urethral dysfunction in causing incontinence.

Secondly, to achieve complete bladder emptying, we have abandoned routine sphincterotomy in patients undergoing the implantation of an AUS (or a cystoplasty) in favour of CISC. This is because we found that sphincterotomy did not always allow complete bladder emptying, particularly in patients undergoing a simultaneous cystoplasy. CISC was required fairly often. We also found that unless a patient had a particularly high sphincteric resistance, judged by a large residual urine volume in the face of a high detrusor pressure, in which case spontaneous voiding post-operatively was extremely unlikely, the correlation between the ability to void pre-operatively and the ability to void completely post-operatively was poor. Rather than use routine sphincterotomy before implantation of an AUS, we now wait and see how well a patient will void and then use CISC if indicated.

The third change has been in our approach to the surgical treatment of patients with the intermediate type of dysfunction. Our approach to the other 2 types has not changed. The contractile type rarely requires surgery because most patients respond to treatment with oxybutynin (78% in our own unpublished experience). When surgery is indicated a "clam" ileocystoplasty is performed. The acontractile type of dysfunction is uncommon but SWI in patients with this type of dysfunction is often disabling and usually requires implantation of an AUS to control it.

The intermediate type is more complicated because of the combination of the detrusor problem and the sphincter problem, each of which may warrant surgical intervention in its own right. Thus, when surgery is indicated, patients in this group almost always need a cystoplasty for detrusor dysfunction and often an AUS for sphincter weakness as well (although a few—about 6%—with unusually low detrusor pressures, large residual urine volumes and troublesome SWI will be satisfactorily treated with an AUS alone). Those with more marked degrees of sphincteric resistance who can be expected not to have SWI postoperatively have a cystoplasty alone and use CISC to achive bladder emptying thereafter. (Nonetheless, in about 10% an AUS will subsequently prove to be necessary). Those who would be expected to have significant SWI if a cystoplasty alone was performed have an AUS as well. However, because the degree of sphincter weakness after correcting the detrusor abnormality is unpredictable (as discussed above), we implant only the cuff at the time of cystoplasty, implanting the other AUS components if necessary to achieve complete continence at a later date.

The rationale for the "clam and a cuff" approach rather than simultaneous implantation of the whole device, or alternatively to wait and see if an AUS is necessary, is that the difficult and surgically traumatic part of implanting an AUS is in the placement of the cuff, particularly after a previous cystoplasty and especially in female patients. If the cuff is in place, implantation of the remainder of the AUS components is a simple subcutaneous procedure through a small groin incision. On the other hand, the "clam and a cuff" approach avoids the need to reopen the pelvis to implant an AUS *de novo* in those patients (at least 43% and probably nearer 60%) who would have significant SWI after a cystoplasty alone, and avoids the cost of implanting the whole of an AUS, particularly the control pump, which is the most expensive component, unless it is definitely needed.

The risk of infection of an AUS in patients having simultaneous bowel surgery has been the subject of discussion (Nurse and Mundy, 1988). Our experience to date of implantation of artificial sphincters in 105 patients with a neuropathic bladder is that the infection rate of the AUS was 15.5% overall—15.7% in those having an AUS alone and 15.3% in those having an AUS and a simultaneous cystoplasty. These results suggest that simultaneous bowel surgery is not a significant risk factor for AUS infection but that neuropathy itself is, because in the absence of neuropathy or other rick factors (95 patients) the AUS infection rate was only 2%, again whether or not there was simultaneous bowel surgery. This raises the question as to whether or not a cystoplasty in conjunction with a bladder neck or urethral suspension procedure might be as effective and, because the risk of AUS infection is eliminated, more satisfactory than the "clam and a cuff" approach. This question has yet to be answered by a prospective trial comparing the 2 approaches.

We conclude that the intermediate type of lower urinary tract dysfunction is the commonest type in congenital neuropathy; that acontractile dysfunction is less common than previously thought; that most patients requiring surgical intervention will have intermediate dysfunction; that most patients who require surgical treatment will therefore require a cystoplasty alone or in conjunction with implantation of an AUS; and that implantation of an AUS alone is rarely indicated. We suggest that routine sphincterotomy prior to implantation of an AUS is best avoided, using CISC as required instead. Finally, we recommend the "clam and a cuff" approach for those with intermediate neuropathic dysfunction who have a significant degree of SWI, since this corrects the principal abnormality—in the bladder—and also allows implantation of the remainder of the device by means of a simple subcutaneous procedure if it proves necessary. This recommendation will need to be qualified if trial of cystoplasty with simultaneous bladder neck or urethral suspension proves just as satisfactory.

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# Follow-up Results with the Stamey Operation for Stress Incontinence of Urine

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Summary—Medium-term results are reported in 100 patients who had a Stamey operation for genuine stress incontinence. The results were good in 72, improved in 8 and 20 were failures when assessed clinically and with pad tests. Most of the failures occurred in the first post-operative year. A repeat Stamey operation was easy and the results have been good in 7 of the 8 cases. Bladder outflow obstruction, urinary infection and wound sepsis were not a problem.

Although Stamey (1973, 1980) reported a 91% success rate with endoscopic bladder neck suspension for stress incontinence of urine, other authors (Mundy, 1983; Gillon and Stanton, 1984) have been disappointed with their short-term results. There is little in the urological literature on longer-term results.

## Patients and Methods

During the last 7 years, 100 Stamey operations have been performed, with a 5-year follow-up in half of these cases. The technique used was similar to that of Stamey (1973) with the minor modifications reported by Ashken *et al.* (1984) and Ashken (1987). The author prefers passing the Stamey needle downwards from the suprapubic incision to the vaginal incision rather than upwards as described by Mundy (1983) or using the double pronged needle recommended by Shah (Jones *et al.*, 1989). It is fundamental to the success of the operation that the needle is sited at the level of the bladder neck and not more distally alongside the proximal or mid-urethra. This avoids later kinking of the urethra which would predispose to mechanical bladder outflow obstruction and possibly an increased incidence of post-operative detrusor instability.

Lengths of 1-cm silastic tube buffers have been used on the loop of all of the nylon sutures to reduce cheese wiring through the pelvic fascia and in some cases at the level of the rectus sheath.

## Results

The results were assessed both clinically and with pad tests and were good in 72 patients; incontinence improved in a further 8 but 20 remained incontinent; 12 of the 20 failures occurred within the first year, 3 during the second, 1 during the third, 1 during the fourth and 3 during the fifth post-operative years. In 12 of these 20 failures there had been previous gynaecological operations for urinary incontinence; in the remaining 8 failures, the Stamey procedure had been the first operation for incontinence. A repeat Stamey operation was easy and has been done in 8 of these 20 cases between 1983 and 1988; so far, the results have been good in 7. Of the 20 failures, 4 were unexpected, 3 had a chronic cough, 6 had detrusor instability, 1 had a unilateral stitch and 6 had other pathologies such as an irradiated bladder, neurological disease or previous injection of the bladder neck with Teflon.

The only other significant complication was temporary suprapubic pain in 13 patients, probably due to a nerve entrapment by the nylon suture. Other rarer complications are listed in the Table. Urinary infection and wound sepsis were not a problem.

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**Table** Complications

| | | |
|---|---|---|
| Recurrent stress incontinence | | 20 |
| Unilateral stitch | | 2 |
| Suprapubic pain: | right | 9 |
| | left | 4 |
| Nylon loop suture removed | | 2 |
| Home with suprapubic catheter | | 4 |
| Chronic retention: I.S.C. | | 1 |
| Urinary tract infection | | 1 |
| Pulmonary embolism | | 1 |
| Wound sepsis | | 0 |

## Discussion

These medium-term results for the Stamey operation are satisfactory rather than excellent, but are comparable to results reported by Stanton (1988) using the Marshall-Marchetti-Krantz colposuspension in 525 cases. There was a 5-year follow-up in 40 patients with a 90% subjective cure rate but a 75% objective cure rate. Post-operative urodynamic studies did not show any long-term evidence of bladder outflow obstruction and this has been confirmed by the videourodynamic assessment of the Stamey procedure by English and Fowler (1988). The absence of wound infection was probably due to peri-operative gentamicin and Flagyl and the use of the inert silastic tube buffers rather than Dacron, which is a woven material. Several authors have reported a suture infection rate of 4 to 16% when using Dacron buffers (Mundy, 1983; Diaz *et al.*, 1984; Fleischer *et al.*, 1984; Huland and Butcher, 1984; Jones *et al.*, 1989; Kirkby and Whiteway, 1989).

Most of the failures were in the first post-operative year. A repeat Stamey operation was both easy and effective, although Wujanto and O'Reilly (1989) reported failures in 3 repeat Stamey operations and recommended that such patients should proceed to an alternative operation such as colposuspension. The failures are usually due to the nylon suture snapping or to the loop and buffer cutting through the pubocervical fascia. In recent cases, not included in the present series, the author has followed the recommendation of Kirby and Whiteway (1989), mounting the number 2 nylon suture on to a needle and picking up both the endopelvic fascia and vaginal dermis. This is the same tissue used for urethral support in the Burch (1961) colposuspension and, to date, the results have been good.

The Stamey operation gives satisfactory medium-term results in patients with genuine stress incontinence. Complications are rare and a repeat Stamey operation can be recommended, particularly when the initial failure was not immediate.

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# The Stamey Endoscopic Bladder Neck Suspension in the Elderly

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Summary—The Stamey procedure was performed on 21 women aged 65 to 81 years; 17 were cured (completely dry) or significantly improved (maximum 1 pad/day). Urethral length was significantly increased by the operation but maximum urethral pressure and maximum flow rate were unchanged. Complications were few.

The Stamey procedure is highly effective in the treatment of genuine stress incontinence (Stamey, 1981; Green *et al.*, 1986). It has the advantage of being a relatively minor procedure with a short operating time, little post-operative pain and brief hospitalisation. It offers much to the elderly woman who requires surgical correction of genuine stress incontinence.

## Patients and Methods

A series of 21 women aged 65 to 81 years had a Stamey endoscopic bladder neck suspension between 1983 and 1988. Assessment, initially as an out-patient, allowed stress incontinence to be witnessed and a reducing diet to be recommended if the patient was overweight. Full urodynamic testing was performed pre-operatively in each case.

Twelve patients complained of stress incontinence alone, 7 had urgency and stress incontinence and 2 had a continuous leak of urine. Urodynamic studies confirmed genuine stress incontinence in 15 patients and mixed stress incontinence and detrusor instability in 4. The 2 patients complaining of continuous incontinence had weak sphincters and hypocompliant bladders (post-radiotherapy and following abdominoperineal resection).

The Stamey procedure was the primary incontinence operation in 15 cases; 4 patients had undergone 1 previous operation for incontinence and 2 others had had 3 procedures. The urine was sterile at the time of operation in each case.

The operative technique was as described by Stamey (1981) with minor changes only. The patient was placed in the lithotomy position. A 16 F urethral catheter was inserted and the balloon inflated. The bladder neck was identified and a small transverse vaginal incision made in the vaginal mucosa at that level on each side. The vaginal mucosa was undermined to create a small pocket to accommodate the urethral buttress. The abdominal incisions were made and a straight Stamey needle passed directly from the medial edge of one abdominal wound, down the back of the symphysis pubis and through the medial edge of the vaginal incision on the same side. Each pass of the needle was checked endoscopically to ensure that the bladder was not entered. A No. 2 nylon suture was pulled through. The needle was passed 1 cm lateral to the first and a sterile carbon fibre buttress (or 1-cm length of Silastic tubing in earlier cases) mounted on to the vaginal end of the suture before the loop was completed. A 1-cm length of sterile Silastic tubing was also mounted on to the suture above the rectus sheath to act as a buttress. When the contralateral suture had been sited the bladder was filled so that an "incontinent jet" was produced. Elevation of the sutures stopped the urinary leak and the sutures were tightened to maintain this tension.

A Bonano suprapubic catheter was used until the patient was voiding successfully. The average hospital stay was 5 days.

Pre- and post-operative urodynamic results were compared and the paired *t* test applied where appropriate. All terms used in this study conform

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to the recommendations of the International Continence Society (1984).

## Results

All but 4 patients attended for repeat urodynamic testing within 1 year of the operation. Of the 4 who did not attend, 3 died of unrelated causes and 1 emigrated. The remainder were followed up by yearly review in the out-patient department. The length of follow-up was 9 months to 5 years. If patients had not been seen within 1 year they were asked to attend for current symptomatic appraisal.

Fourteen patients did not complain of urinary incontinence after the operation and were defined as cured; 3 were much improved in that they no longer considered their urinary leak to be significant and required at most 1 pad /day. These 3 patients were suffering from combined stress incontinence and detrusor instability. Surgery cured their stress incontinence but urgency and urge incontinence remained unchanged and required anticholinergic therapy before further symptomatic relief was achieved.

Post-operative urodynamic tests showed a significant increase in urethral length ($P=0.004$) (Table 1) but there was no difference in maximal urethral pressure ($P=0.87$) (Table 2) or maximum flow rate ($P=0.09$) (Table 3) when the paired $t$ test was applied.

Three patients had 100 to 140 ml of residual urine after voiding. None complained of voiding difficulties; 2 had voided by straining without detrusor contraction pre-operatively.

Post-operative complications were few. One stitch abscess required surgical drainage and a patient who complained of persistent pain at the site of a suture obtained permanent relief from a single injection of local anaesthetic. Another patient had prolonged voiding difficulties and deterioration in her health meant that an indwelling urethral catheter was required. Detrusor instability developed post-operatively in only 1 case.

The operation failed in 4 cases. In 1 patient who had had 3 previous anterior repairs, a grossly scarred anterior vaginal wall was holding open the bladder neck. Two other patients had been noted to have hypocompliant bladders pre-operatively. One patient had urinary incontinence following radiotherapy for Stage III carcinoma of the cervix; she developed a vesicovaginal fistula from rapidly progressing disease and died within 1 year. Another patient was incontinent following abdominoperineal resection for carcinoma of the anus. This patient had post-operative voiding problems and required long-term catheterisation. The fourth patient who failed had no "mitigating" factors and awaits further treatment.

**Table 1** Comparison of Pre- and Post-operative Urethral Length

| *Urethral length (cm)* | *Pre-op* | *Post-op* |
|---|---|---|
| Range | 1.3–4.2 | 2.1–4.5 |
| Mean | 2.74 | 3.14 |

$P=0.004$

**Table 2** Comparison of Pre- and Post-operative Maximum Urethral Pressure

| *Maximum urethral pressure (cm $H_2O$)* | *Pre-op* | *Post-op* |
|---|---|---|
| Range | 13–42 | 13–60 |
| Mean | 23.1 | 23.8 |

$P=0.87$

**Table 3** Comparison of Pre- and Post-operative Maximum Flow Rate

| *Flow rate (ml/s)* | *Pre-op* | *Post-op* |
|---|---|---|
| Range | 9.3–47 | 8–24 |
| Mean | 19.97 | 14.87 |

$P=0.09$

## Discussion

It is recognised that maximum urethral pressure (MUP) falls with age and to a greater extent in women suffering from stress incontinence. Pre-operative MUP measurements proved remarkably low in this series (mean value 23.1 cm $H_2O$). Considering also the poor tissue oestrogenisation of the post-menopausal women, it was felt that the results of surgery might be poor. Good symptomatic relief was reported post-operatively, with 81% of patients completely dry or much improved without a significant rise in MUP measurements. Maximum flow rates were also normal. These results confirm earlier reports (Massey *et al.*, 1987) that the Stamey procedure is not obstructive. The stress urethral profile returned to normal in 9 cases. However, with such low urethral pressures most results were difficult to interpret and were defined as equivocal. It is noteworthy that of 5 patients with MUP measurements of 20 cm $H_2O$ or less, 4 do not complain of stress incontinence.

The Stamey endoscopic bladder neck suspension is an effective procedure for the correction of stress incontinence in the elderly, giving a cure rate in this series which is compatible with that obtained for younger age groups (Ashken *et al.*, 1984; Huland and Bucher, 1985; Kirby and Whiteway, 1989; Kondo *et al.*, 1989). The low incidence of side effects has been noted by others (Jackson, 1986) and the procedure is therefore recommended when surgery is required to cure stress incontinence in the elderly woman.

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# Diagnosis of Clinically Occult Bladder Cancer by *in vivo* Staining with Methylene Blue

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Summary—*In vivo* staining of the bladder mucosa with 0.1% methylene blue in normal saline was performed on 23 randomly selected patients with known and previously treated transitional cell tumours of the bladder in whom routine check cystoscopy failed to demonstrate any mucosal abnormality. In 21 patients differential staining of the bladder mucosa resulted, with no mucosal staining in 2. Cold cup biopsies were obtained from stained as well as unstained areas. Although positive staining did not prove the presence of a pre-malignant or malignant area, lack of staining was more likely to exclude mucosal abnormalities.

Pre-malignant or flat endophytic neoplastic lesions of the bladder can be difficult to recognise by conventional cystoscopy and random biopsies of the bladder mucosa are frequently employed by urologists to evaluate the general state of bladder epithelium and to monitor the course of the disease. However, random biopsies from an apparently normal area can leave the clinician with considerable uncertainty because an abnormal area may still remain undetected. Chemical markers which would be selectively taken up by malignant bladder epithelium have been used in the past. Whitmore *et al.* (1984) described ultraviolet fluorescence in malignant bladder epithelium following the administration of oral tetracycline. Similarly, haematoporphyrin derivative was used for detection as well as phototherapy of carcinoma of bladder (Kelly and Snell, 1976). Although these methods showed promise, they did not achieve popularity in day-to-day urological practice.

Gill *et al.* (1984) described their method of ionic dye chromocystoscopy using intravesical methylene blue in normal saline for selective staining of bladder tumours. Their encouraging results prompted us to evaluate this technique and its usefulness in clinical practice.

## Patients and Methods

This prospective study was undertaken on 30 patients selected at random from a pool of known patients with urothelial neoplasia who attended St Peter's Group of Hospitals for regular follow-up cystoscopies. Only those patients with no evidence of recurrent tumours in the bladder on cystoscopy and with no past history of radiotherapy to the bladder were investigated, using the technique described below. Informed verbal consent was obtained from all patients.

After conventional cystoscopy, the bladder was catheterised with a 16F Foley latex catheter and 0.1% solution of methylene blue in 0.9% saline was instilled into the bladder by gravity fill. In the first 7 patients the bladder was filled with different volumes and at different filling pressures. Overfilling the bladder too quickly, and at a high pressure, resulted in blue staining of the entire mucosa with deeply stained islands which probably represented areas of mucosal injury. Underfilling caused staining of only the trigone and the posterior bladder wall, possibly due to inadequate contact of the dye with the rest of the bladder mucosa. Since these findings were not evaluable, these 7 patients were excluded from the results. In the other 23 patients we used the method described by Gill *et al.* (1984), using a standard bladder filling technique at a pressure not exceeding 20 cm of water, up to a

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maximum volume of 400 ml. In most cases the bladder held less than 300 ml at less than 20 cm of pressure. After bladder filling the catheter was spigotted and 5 min later the bladder was emptied. The bladder was then rinsed 3 times with 100 ml normal saline and the catheter removed.

Cystoscopy was repeated in all patients. This was followed by examination of the stained areas with a contact microcystoscope (Storz Catalogue No. 26156 BU), which can provide a magnification up to ×150 on contact viewing. Multiple cold cup biopsies (average 3) were taken from stained as well as unstained areas. The specimens were fixed in formalin and the stained and unstained specimens labelled separately as "A" and "B". All sections were examined by a histopathologist (M.C.P.), who was unaware of the study details.

## Results

In 2 patients the entire mucosa remained unstained and multiple biopsies showed benign transitional cell epithelium on histological examination. In the remaining 21 patients cystoscopy revealed patches of blue-stained mucosa amidst unstained areas, ranging from spotty blue to deep blue staining; 67 biopsy specimens were obtained from the stained areas in these 21 patients; 33 (49%) showed a normal transitional epithelium. These included 16 specimens from 6 patients in whom all of the specimens from stained areas failed to reveal any urothelial pathology; 34 biopsies (51%) from stained areas in the other 15 patients demonstrated epithelial abnormalities ranging from dysplasia to invasive carcinoma in 1 or more specimens (Table); 3 of these biopsies from 2 patients showed evidence of carcinoma *in situ* and in another patient 2 biopsies revealed invasive transitional cell carcinoma.

Staining did not interfere with the epithelial morphological detail and blue staining was not visible on histological examination of stained sections.

A total of 83 biopsies were obtained from the unstained areas. In 75 of these (90%) the urothelium was benign.

Contact microcystoscopy was performed in 13 patients. This was not a helpful exercise because the interpretation of cytological detail was not possible on contact viewing at high magnification. Therefore this part of the procedure was abandoned in the remaining 10 patients.

## Discussion

Several ionic histochemical dyes (cationic methylene blue, toluidine blue, alcian blue, anionic trypan blue, congo red and Evans blue) are known to adhere to abnormal urothelial surfaces *in vivo* but not to the normal urothelium. This is due to abnormal crystal adherence to the surface of the abnormal cell (Gill *et al.*, 1981). Urothelial tumour cells have also been shown to be abnormally permeable to sodium and water (Fellows, 1972; Hicks *et al.*, 1974). Combining the 2 concepts, Gill *et al.* (1984) hypothesised that cationic dyes such as methylene blue in normal saline would adhere selectively to the surface of urothelial tumours, gain entry into the cells through their abnormal permeability to sodium and water, and combine with

**Table** Analysis of Histology Results

| *Histological findings* | *Stained areas* *No. of biopsies* | *Stained areas* *No. of patients* | *Unstained areas* *No. of biopsies* | *Unstained areas* *No. of patients* |
|---|---|---|---|---|
| Hyperplasia | — | — | 2 | 2 |
| Dysplasia | 12 | 8 | 3 | 3 |
| Loss of surface epithelium | 7 | 5 | 1 | 1 |
| Carcinoma *in situ* | 3 | 2 | — | — |
| PTa G1 transitional cell carcinoma | 7 | 5 | 2 | 2 |
| PTa G2 transitional cell carcinoma | 3 | 3 | — | — |
| PT2 G2 transitional cell carcinoma | 2 | 1 | — | — |
| Abnormal | 34<br>(51%) | 15 | 8<br>(10%) | 8 |
| Normal | 33<br>(49%) | 16 | 75<br>(90%) | 23 |
| Total | 67 | 21 | 83 | 23 |

negatively charged nucleic acids. They extended this hypothesis by performing *in vivo* urothelial surface histology with the use of a contact magnifying cystoscope (Gill *et al.*, 1983). Their results showed that 92% of patients demonstrated selective staining of bladder tumours and false positivity was seen only in those patients who had had previous intravesical or systemic chemotherapy (Gill and Strauss, 1984). However, it was not clear how many of these patients would have been diagnosed by conventional cystoscopy without chromatin staining.

The aim of the present study was to establish whether the method could be used to map premalignant or malignant areas which are not recognised by cystoscopy alone. Thus only patients with normal cystoscopic appearances were investigated by this procedure.

The results showed that only half of the biopsies from stained areas revealed evidence of epithelial abnormality, ranging from dysplasia to invasive carcinoma. If one bears in mind the fact that these biopsies were obtained from bladders which were considered normal on conventional cystoscopy, this finding assumes significance. Of greater significance is the finding that 90% of biopsy specimens from unstained areas showed no evidence of epithelial abnormality (Table). Therefore, whilst positive staining does not confirm the presence of an abnormal area, lack of staining is more likely to exclude an epithelial abnormality. The latter observation could have useful clinical implications, particularly in patients with multifocal urothelial neoplasia which may not be obvious on conventional cystoscopy. Mapping out unstained areas could reveal the extent of normal mucosa and restrict the clinician to biopsy only the stained areas, thus making the latter procedure less random. This conclusion is also supported by the finding that chromatin staining helped to detect abnormalities from apparently normal mucosa in 65% of our patients compared with a "pick up" rate of only 37% reported by Smith *et al.* (1983) without the use of the dye.

In their description of microscopic cystoscopy, Gill *et al.* (1983) observed: "Cytological detail is resoluble with the highest magnification of × 150. With more experience and refinement of the procedure we believe that *in vivo* urothelial histology should enhance the ability of the urologist to diagnose and treat diseases of abnormal malignant and benign epithelium". In our experience with 13 patients, however, resolution of cytological detail was impossible on contact magnification and the procedure was abandoned in the last 10 patients.

Larger studies are needed in this field. However, in this small study we found the procedure to be both simple and safe.

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# Immunohistochemical Staining with Monoclonal Antibody 32–2B to Desmosomal Glycoprotein 1

## Its Role in the Histological Assessment of Urothelial Carcinomas

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Summary—A series of transitional cell carcinomas of bladder were stained immunohistochemically with the monoclonal antibody, 32–2B, to desmosomal glycoprotein 1. All of the sections showed positive staining with the antibody. Assessment of staining intensity, by 3 independent examiners, revealed a strong negative correlation between density of desmosomal staining and degree of invasion ($P=0.012$). Nests of strongly staining cells were identified in several invasive tumours, possibly indicating early squamous differentiation. Invasive tumour cells in the subepithelial stroma also stained strongly with the antibody. Correlation with clinical course, however, revealed no significant association between desmosomal staining and the incidence of recurrence or progression.

It is suggested that staining with this antibody may be of value in detecting both stromal invasion and early squamous differentiation of transitional cell carcinomas. Both this and previous studies emphasise the value of this antibody as an epithelial marker in neoplasia.

Desmosomes or *maculae adherentes* are intercellular adhesive junctions present in epithelia (Cowin and Garrod, 1983; Cowin *et al.*, 1984; Moll *et al.*, 1986), cardiac muscle (Franke *et al.*, 1982; Cowin *et al.*, 1984), the arachnoid and pia of the meninges (Alcolado *et al.*, 1987) and follicular dendritic cells of lymph nodes (Jones and Garrod, 1989). Their structure and biochemistry have been reviewed by Cowin *et al.* (1984), Garrod (1986) and Garrod *et al.* (1989).

Several ultrastructural morphometric analyses have investigated a possible association between size and numbers of desmosomes and malignant transformation in urothelium. Pauli *et al.* (1978) found no correlation between numbers of desmosomes and tumour aggressiveness of transitional cell carcinomas of rat urinary bladder induced by N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT). On the other hand, Alroy *et al.* (1981) showed that the numbers of desmosomes were decreased in comparison with normal epithelium in invasive transitional cell carcinoma of human bladder.

Light microscopic visualisation of desmosomal immunoreactivity would potentially provide further information on desmosomal alterations in malignancy. Monoclonal antibodies and polyclonal antisera raised against desmosomal components have permitted their immunohistochemical visualisation at the light microscope level in frozen section material (Franke *et al.*, 1983; Osborn and Weber, 1985; Moll *et al.*, 1986; Parrish *et al.*, 1987). More recently the production of a monoclonal antibody, 32–2B, to one of the major desmosomal components, desmosomal glycoprotein 1 (dg1), has enabled visualisation of the latter in formalin-fixed, paraffin-embedded tissue sections (Vilela *et al.*, 1987).

As part of a larger investigation of immunohistochemical staining characteristics of benign and malignant urothelial tissue (Conn *et al.*, 1987, 1988),

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the monoclonal antibody 32–2B has been used with a large number of superficial and invasive urothelial carcinomas in order to assess their staining patterns in developing malignancy, their relationship with prognosis and their potential value in routine histopathology.

## Materials and Methods

A series of 84 transitional cell carcinomas of the bladder (69 superficial, 15 invasive) which were initially resected in the Queen Elizabeth Hospital, Birmingham, between 1980 and 1982 were studied. All of the blocks had been fixed in 10% formal saline and wax embedded. Sections of 3 μm thickness were cut from each tumour block and processed for immunohistochemical staining as described below. Hospital case records and cancer registry follow-up notes were scrutinised to obtain 5-year follow-up information on recurrence and disease progression for all patients. Progression was defined as an increase in pT category (UICC, 1978) from superficial (pTa or pT1) to muscle-invasive disease (pT2+) or the development of distant metastases.

### *Immunohistochemistry*

The monoclonal antibody 32–2B is an IgG2a class immunoglobulin raised against dg1 as described previously (Vilela *et al.*, 1987) and was used at a concentration of 19 μg/ml in tissue culture medium. This antibody is now commercially available from Sanbio bv. Immunohistochemical staining was by the avidin-biotin complex (ABC) method (Hsu *et al.*, 1981). Following dewaxing and rehydration, the sections were treated with 1% $H_2O_2$ in methanol to block endogenous peroxidase activity. They were then incubated in 0.1% trypsin (Type II: crude, from porcine pancreas, Sigma) in 0.1% $CaCl_2$ at 37°C for 10 to 15 min, washed in water and then in Tris-buffered saline (TBS; 0.5M Tris/HCl, pH 7.6, diluted 1 : 10 with 0.15M NaCl). Following this the sections were treated consecutively with the monoclonal antibody 32–2B, with biotinylated rabbit anti-mouse Ig and then with the avidin-biotin complex (ABC kit, DAKO). Each incubation was for 30 min and was followed by three 5-min washes with TBS. Peroxidase activity was visualised using 3,3′-diaminobenzidine.

### *Classification and Scoring of Histological Sections*

Haematoxylin and eosin sections were examined by a histopathologist (J.C.) and each tumour classified according to stromal or muscular invasion (UICC, 1978) and degree of histological differentiation (Mostofi, 1973). The sections stained with the anti-desmosomal antibody were examined independently by 3 of the authors (I.G.C., M.J.V. and D.R.G.) without knowledge of the histological assessment or subsequent clinical course of the patient. Each tumour was given a score of 1 to 3 depending on the overall staining intensity of the section: 1 = low density (Fig. 1), 2 = intermediate density (Fig. 2) and 3 = high density (Fig. 3).

## Results

Sections from 8 tumours were either too small or traumatised, so the study was performed on the remaining 76 tumours. All of the sections showed positive staining for the anti-desmosomal antibody. At high magnification the staining was seen to be punctate in nature and was situated at the cell contacts. Denser staining was often seen in the luminal cells. Sections from several tumours had small nests of very intense desmosomal staining (Fig. 4) and, on review of the haematoxylin and eosin sections, these areas corresponded to nests of squamous differentiation within transitional cell carcinomas. Strong staining was also seen in invasive tumour nests in the subepithelial stroma (Fig. 5).

There was a high degree of inter-observer correlation in the assessment of staining intensity.

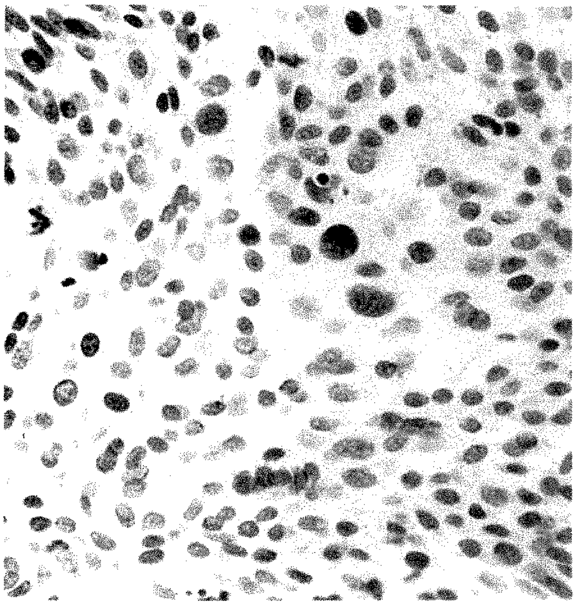

**Fig. 1** Poorly differentiated transitional cell carcinoma. Low density desmosomal staining. (Anti-desmosomal antibody 32–2B × 150).

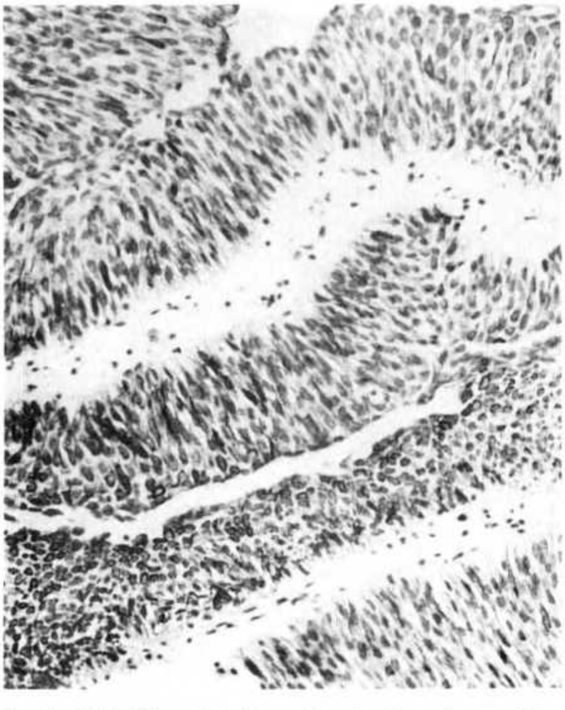

**Fig. 2** Well differentiated transitional cell carcinoma. Intermediate density desmosomal staining. (Anti-desmosomal antibody 32–2B × 150).

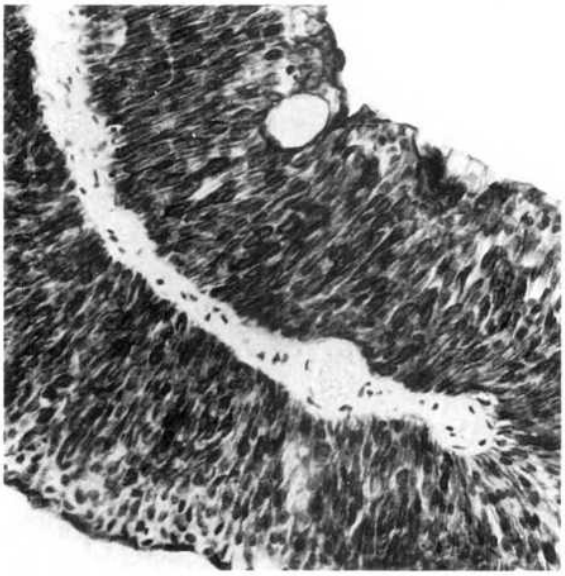

**Fig. 3** Well differentiated transitional cell carcinoma. High density desmosomal staining. (Anti-desmosomal antibody 32–2B × 150).

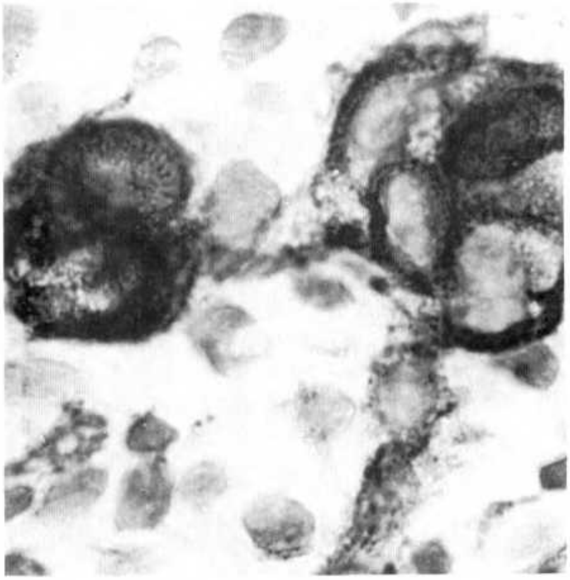

**Fig. 4** Poorly differentiated transitional cell carcinoma. Strong staining of nests of cells possibly indicating early squamous differentiation. (Anti-desmosomal antibody 32–2B × 400).

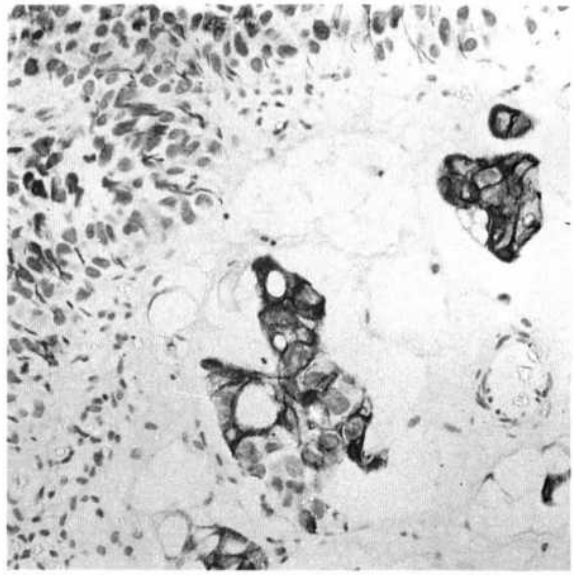

**Fig. 5** Poorly differentiated transitional cell carcinoma. Strong staining of invasive nests in the sub-epithelial stroma. (Anti-desmosomal antibody 32–2B × 150).

Of the 76 tumours suitable for study, complete agreement by all 3 examiners was achieved in 44 (58%) and by 2 of 3 examiners in 31 (41%). In the latter cases the agreed score was used. In only 1 tumour was there complete disagreement. This tumour was excluded from the analysis. There was a strong correlation between density of desmosomal staining and pT category (Table 1). Of the superficial non-invasive (pTa) tumours, 27 of 36 (75%) had intermediate or high density staining, whereas of the muscle-invasive tumours 9 of 13 (69%) had low density staining. However, there was no correlation between staining and histological grade (Table 2).

The association between density of desmosomal staining of the 63 superficial (pTa and pT1) tumours and their subsequent clinical course was assessed (Table 3). This revealed no significant association between desmosomal staining and the incidence of recurrence or progression, although those tumours with high desmosomal density (score = 3) had a lower incidence of recurrence compared with the other 2 groups (chi-square (1df) = 4.0; $P = 0.045$).

## Discussion

Examination of the tumours stained by this method showed a wide variation in staining intensity. There was a good negative correlation between desmosomal staining and the degree of invasion of the tumour. It failed, however, to confirm any relationship between desmosomal staining and the incidence of either recurrence or progression of superficial tumours. As the antibody is directed against a glycoprotein component of desmosomal junctions, it is reasonable to suggest that the level of staining intensity may be representative of desmosomal numbers. If this assumption is made, the findings of this study are in agreement with the results of quantitative electron microscope studies of desmosomal numbers in human urothelial carcinomas (Alroy *et al.*, 1981). This study reported a decrease is desmosome numbers in invasive tumours compared with superficial papillary lesions. Similarly, the lack of a significant association between desmosomal staining and progression may concur with previous conclusions of Pauli *et al.* (1983) that a decrease in intercellular adhesion is not a prerequisite of invasiveness. In this study, however, the desmosomal staining of recurrent or progressive tumours was not examined.

**Table 1** Anti-desmosomal Antibody Score and pT Category

| | *Desmosomal score* | | |
|---|---|---|---|
| | *1* | *2* | *3* |
| *pTa* | 9 | 19 | 8 |
| *pT1* | 16 | 7 | 3 |
| *pT2+* | 9 | 4 | 0 |

(Chi-square (4df) = 12.8, $P = 0.012$)

**Table 2** Anti-desmosomal Antibody Score and Histological Grade

| | *Desmosomal score* | | |
|---|---|---|---|
| | *1* | *2* | *3* |
| *G1* | 10 | 9 | 5 |
| *G2* | 12 | 12 | 3 |
| *G3* | 12 | 9 | 3 |

(Chi-square (4df) = 1.3, $P = 0.86$)

**Table 3** Recurrence and Progression of Superficial Tumours

| | *Desmosomal score* | | |
|---|---|---|---|
| | *1* | *2* | *3* |
| Number recurring (%)* | 21/25 (81) | 21/26 (84) | 6/11 (55) |
| Number progressing (%)† | 5/25 (20) | 4/26 (15) | 2/11 (18) |

*$P = 0.13$
†$P = 0.91$

The importance of histological grade in the prognostic assessment of urothelial tumours has been stressed recently (Torti *et al.*, 1987; Abel, 1988). It is perhaps surprising that the poor cellular differentiation of high grade tumours does not correlate with reduction in desmosomal staining, since cellular differentiation is associated with increasing maturity and number of desmosomes in normal transitional epithelium (Pauli *et al.*, 1983).

Further examination of the tumours also revealed several other interesting features. The intense staining of isolated nests of cells within areas of relatively low staining intensity was highly suggestive of squamous differentiation. The electron microscope studies of Pauli *et al.* (1977, 1978) also demonstrated increased numbers of desmosomes in such areas. This finding may be of particular clinical importance in the prediction of radiosensitivity of invasive tumours. Invasive nests of tumour cells in the subepithelial stroma stained strongly with the desmosomal antibody. Again, this is similar to findings in previous ultrastructural studies.

It is concluded that staining intensity is not related to subsequent clinical course in superficial bladder tumours but it does appear to be a sensitive indicator of early squamous differentiation and submucosal invasion in transitional cell carcinomas. The tumours stained in this study add to the large number of primary and secondary carcinomas that have shown staining with anti-desmosomal antibodies (Franke *et al.*, 1983; Osborn and Weber, 1985; Moll *et al.*, 1986; Parrish *et al.*, 1987; Vilela *et al.*, 1987; Garrod *et al.*, 1989), emphasising the value of such antibodies as epithelial markers.

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# Defective Interleukin-1 Production of Monocytes in Patients with Bladder Cancer

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Summary—Patients with advanced malignant neoplasms have a variety of abnormal lymphocyte and monocyte functions. We examined the PHA (phytohaemagglutinin) blastogenic response of lymphocytes and interleukin-1 (IL-1) production of monocytes in 40 bladder cancer patients and 16 control subjects. The correlation between the 2 parameters was also studied. The PHA blastogenic response was measured by the incorporation of $^3$H-thymidine into lymphocytes. IL-1 production was assayed by the murine thymocyte $^3$H-thymidine incorporation assay. As a result, the PHA blastogenic response and IL-1 production were significantly lower in the high stage bladder cancer patients compared to the control subjects and low stage patients. However, there was no significant correlation between the 2 parameters.

Furthermore, with the addition of indomethacin, IL-1 production in the control subjects and low stage patients improved to the same degree, but it did not reach the control level in the high stage patients.

There is little dispute that macrophages play an important role in the host defence mechanism against primary and metastatic cancer (Hibbs *et al.*, 1978; Adams and Snyderman, 1979). Many studies have been made on a variety of abnormal monocyte functions in patients with advanced malignant neoplasms. Chemotaxis of monocytes has been shown to be suppressed (Snyderman *et al.*, 1977; Walter and Danielson, 1985), but both phagocytic activity and cytotoxic activity have been shown to be elevated (Jerrels *et al.*, 1979; Mashiba *et al.*, 1981) and suppressed (Mantovani *et al.*, 1980). On the other hand, recent studies have indicated that monocytes produce monokines and contribute to the regulation of immune responses. Monokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF) have been used in cancer treatment. In the treatment of cancer, it is important to understand the immunocompetence of cancer patients. In this study, we estimated the IL-1 production of monocytes by the murine thymocyte $^3$H-thymidine incorporation assay and examined the correlation between the PHA blastogenic response of lymphocytes and IL-1 production of monocytes in bladder cancer patients. We also studied the effects of indomethacin on monocyte IL-1 production.

## Patients and Methods

Forty patients with bladder cancer (mean age 63.4 years) were studied. Histological examination of their tumours indicated transitional cell carcinoma in all cases. Tumour stages were classified according to UICC (1978). Sixteen age-matched control subjects (mean age 62.7 years), whose diagnosis was benign, were studied by the same method. Individuals with chronic or acute infection and those on specific medication were excluded.

### *Mononuclear cell preparation and culture*

Peripheral blood mononuclear cells (PBMC) were separated from freshly drawn heparinised blood by centrifugation over Ficoll-Hypaque gradient. The cells were washed 3 times with RPMI 1640 medium (GIBCO, Grand Island, NY) and suspended at 1 × $10^6$ cells/ml in RPMI medium containing 100 u/ml penicillin, 50 μg/ml streptomycin and 10% fetal calf

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serum (GIBCO) (complete medium). The media and supplements were free of endotoxin as detected by the Limulus assay. Cell cultures were performed in triplicate in 96 well microtitre plates (Nunc). Each well contained $2 \times 10^5$ mononuclear cells in 200 µl complete medium, and 20 µg/ml phytohaemagglutinin P (PHA-P; Difco) was added. The cell cultures were then incubated at 37°C for 72 h in a humidified atmosphere of 5% $CO_2$ in air; 18 h prior to termination, 0.2 µCi of $^3H$-thymidine (5 mCi/mmol, Amersham, Japan) was added to each well. The cells were harvested and the incorporation of thymidine into DNA was measured using a liquid scintillation counter. The results were expressed as mean cpm of triplicate wells.

*Preparation of IL-1 supernatants*

PBMC ($4 \times 10^5$ cells/well) were placed in flat-bottomed microtitre plates (Nunc) and incubated at 37°C for 2 h in a humidified atmosphere of 5% $CO^2$ in air. Non-adherent cells were then removed by vigorous washing. The remaining adherent cells, which were more than 90% non-specific esterase positive, were incubated with 200 µl/well of complete medium and 10 µg/ml lipopolysaccharide (LPS; Difco) at 37°C for 48 h in a humidified atmosphere of 5% $CO^2$ in air. In another group, 1.0 µg/ml indomethacin was also added to the culture before incubation.

*IL-1 assay*

The activity of IL-1 was assayed using thymocytes of C3H/He mice according to the method of Mizel *et al.* (1978). Cell cultures were performed in triplicate in flat-bottomed microtitre plates. Each well contained $1 \times 10^6$ thymocytes in 200 µl of complete medium, 20 µl of the IL-1 source and 2 µg/ml Concanavalin A (Con A; Difco). The cultures were incubated at 37°C for 72 h in a humidified atmosphere of 5% $CO_2$ in air; 18 h prior to termination, 0.5 µCi of $^3H$-thymidine was added to each well. The cells were harvested and the incorporation of thymidine into thymocytes was measured using a liquid scintillation counter. The results were expressed as mean cpm of triplicate wells. The incorporation of $^3H$-thymidine into thymocytes was not affected by the addition of 1.0 µg/ml indomethacin.

*Statistics*

All values were expressed as mean ±SD. They were analysed by one-way analysis of variance and individual comparison was made by the Student-Newman-Keuls test. Regression lines were fitted by the least squares method.

## Results

*PHA response of PBMC in control subjects and bladder cancer patients*

The mean proliferative response was 18800 ± 6400 cpm for the control subjects, 18200 ± 5200 cpm for the low stage patients and 11000 ± 6100 cpm for the high stage patients. The difference between the controls and the high stage patients and between the low stage patients and the high stage patients was statistically significant ($P < 0.01$, $P < 0.01$). However, the difference between the controls and the low stage patients was not significant (Fig. 1).

*IL-1 production of monocytes in control subjects and bladder cancer patients*

The mean IL-1 production was 51700 ±24500 cpm for the control subjects and 47000 ±22300 cpm for

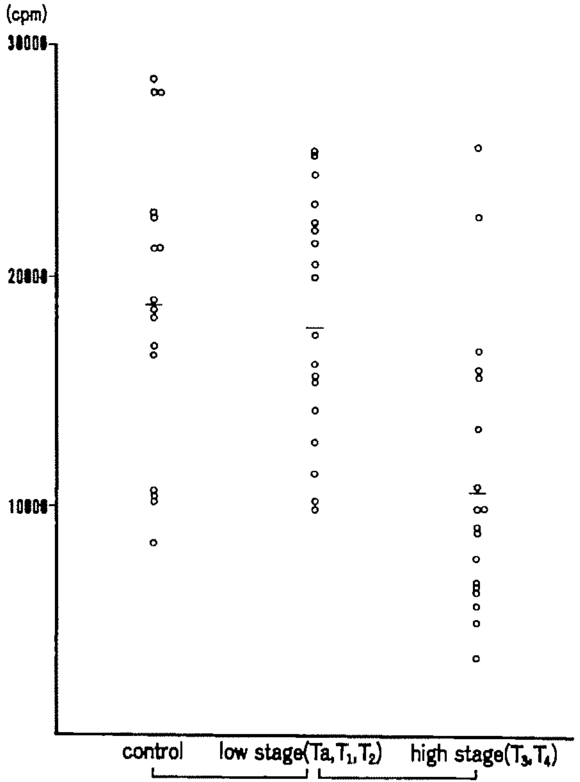

Fig. 1 PHA (20 mg/ml) response of mononuclear cells in controls and bladder cancer patients.

the low stage patients. In contrast, the mean IL-1 production for the high stage patients was 29700 ± 22800 cpm, which was significantly lower than that for both the controls ($P<0.05$) and the low stage patients ($P<0.05$) (Fig. 2).

### *Effects of indomethacin on IL-1 production of monocytes*

When indomethacin was added, the mean IL-1 production was 62700 ±32500 cpm for the control subjects, 52200 ±24600 cpm for the low stage patients and 36400 ±29000 cpm for the high stage patients. By adding indomethacin, IL-1 production in the controls and low stage patients was improved to the same degree. However, it did not reach the control level in the high stage patients (Fig. 3).

### *Correlation between PHA response of PBMC and IL-1 production of monocytes*

There was no significant correlation between the PHA response of PBMC and IL-1 production of monocytes ($r=0.25$, $P=0.06$) (Fig. 4).

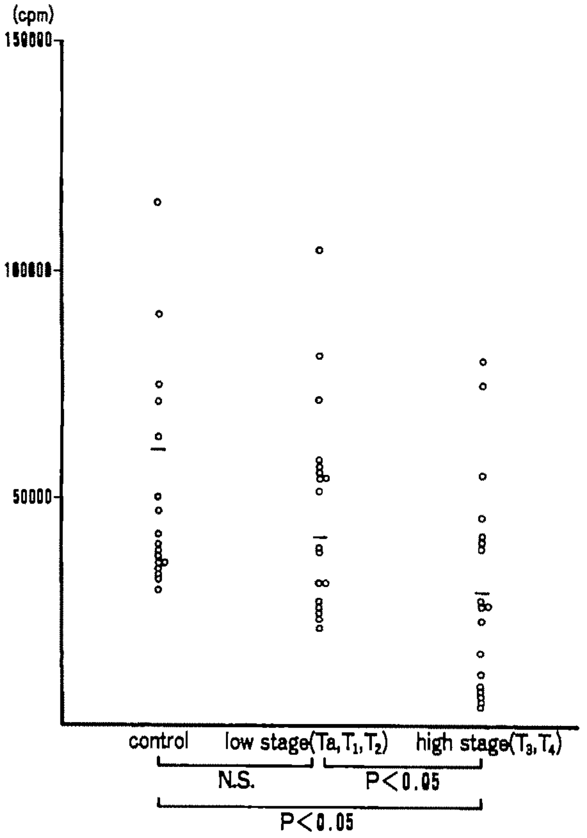

**Fig. 2** IL-1 production of monocytes in controls and bladder cancer patients.

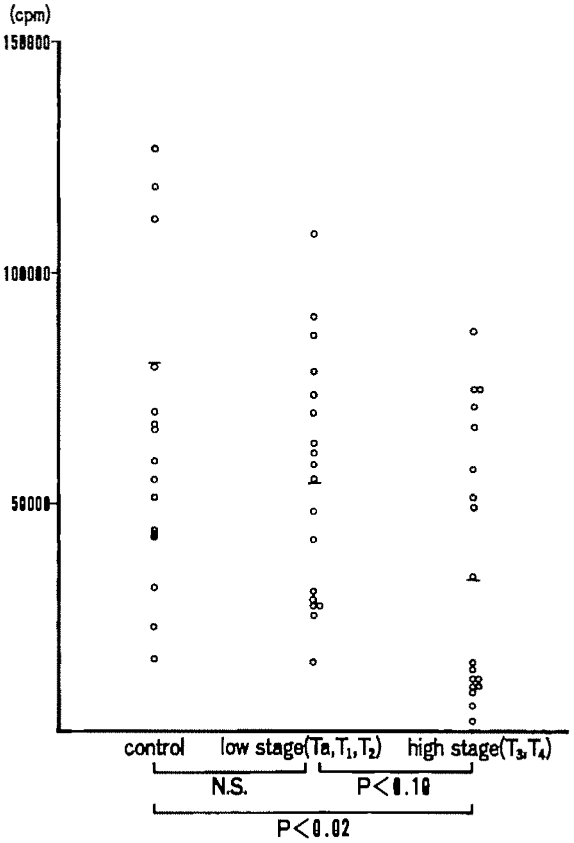

**Fig. 3** Effect of indomethacin on Il-1 production of monocytes in controls and bladder cancer patients.

## Discussion

Macrophages are known to function as scavenger cells with phagocytic and microbicidal activity and as antigen-presenting cells with the role of presenting antigen to antigen-sensitive lymphoid cells. It has recently been found that macrophages also play a central role in the regulation of the cellular and humoral immune response. Some aspects of this regulatory function are mediated by its soluble product, IL-1, which has a molecular weight of 15000 and has two subtypes, $\alpha$ and $\beta$. IL-1 is known to exert a wide variety of effects on immune cells such as the activation of T cells to produce lymphokines, activation of antibody-producing B lymphocytes and stimulation of natural killer cell activity when used in conjunction with interferon or IL-2 (Dinarello, 1985).

There have been some reports regarding IL-1 production of cancer patients. Santos *et al.* (1985) showed that IL-1 production by advanced cancer patients was significantly lower than in normal

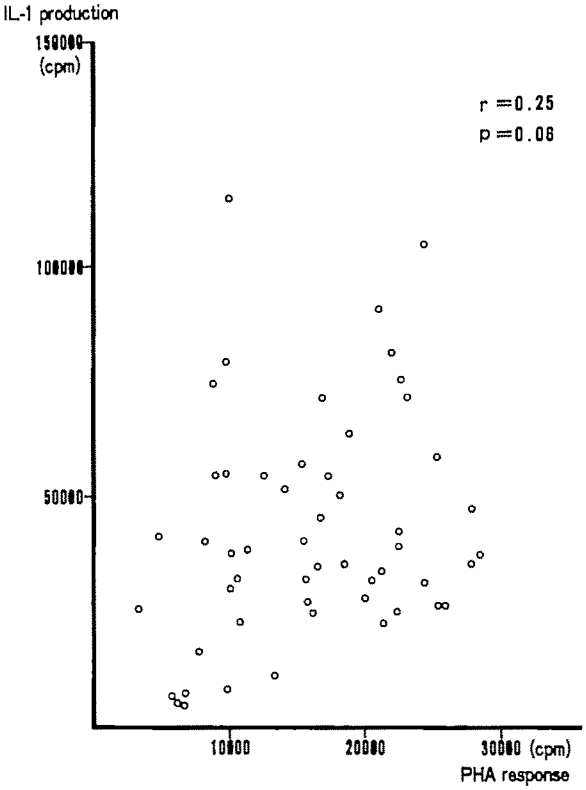

**Fig. 4** Correlation between PHA response of mononuclear cells and Il-1 production of monocytes in controls and bladder cancer patients.

controls. They also observed that depressed blastogenesis with PHA returned to normal when IL-1 was added to mononuclear leukocytes depleted of monocytes. Pollack *et al.* (1983) reported that in many patients with breast cancer, malignant melanoma or colorectal cancer, IL-1 production by monocytes was abnormal. Furthermore, they demonstrated that in each group, IL-1 release was low in patients with early cancer, normal in patients with regional metastasis and low in patients with disseminated cancer. Herman *et al.* (1984) indicated that monocytes from patients with large tumour masses produced considerably less IL-1 than those from controls or patients with small tumour burdens. They found that after treating control or patient monocytes with human leukocyte interferon, IL-1 production was markedly improved. There have been few reports concerning IL-1 production in urological malignant diseases. We found that IL-1 production by bladder cancer patients in the high stage was lower than in control subjects. The PHA blastogenic response of lymphocytes was also low in high stage bladder cancer patients. The PHA blastogenic response is regarded as an expression of T cell function. The low PHA blastogenic response indicates non-specific cellular immunity in bladder cancer patients. However, IL-1 production of monocytes did not correlate with the PHA blastogenic response of lymphocytes. This showed that the low PHA blastogenic response was not caused by the decrease in IL-1 production. Moreover, several factors have been suggested, including intrinsic lymphocyte abnormalities, serum factors and suppressor cells.

Defective IL-1 production can lead to a defective lymphokine cascade with decreased production of IL-2 and interferon-$\gamma$. Lymphokines are needed for the induction of cytotoxic T cells (Gillis *et al.*, 1981), natural killer cells (Suzuki *et al.*, 1983) and lymphokine-activated killer cells (Grimm *et al.*, 1982), which are important in the host defence mechanism against malignancy. IL-1 is also known to be a cytostatic and cytotoxic factor for tumour cells (Lachman *et al.*, 1986). Abnormal IL-1 production may cause the impairment in anti-tumour immunocompetence. However, the mechanisms responsible for the abnormal production of IL-1 by monocytes derived from cancer patients remain unknown. One possibility is the decrease in the frequency of IL-1 producer monocyte subsets. Gilman *et al.* (1982) showed that human monocyte subsets distinguished by surface markers differed in their functional ability to act as accessory cells and produce IL-1, and that Ia positive monocytes produced mainly IL-1. Nagai *et al.* (1986) also found that in Hodgkin's disease, the amount of Ia positive monocytes was decreased.

On the other hand, monocytes have also been identified as one of the suppressor cell systems. Prostaglandin $E_2$ ($PGE_2$), which is one of the soluble mediators produced by monocytes, plays an important role in immunosuppression (Goodwin *et al.*, 1977; Schultz *et al.*, 1978). There have been many reports that peripheral blood monocytes from patients with head and neck cancer (Berlinger, 1984), colon cancer (Charles *et al.*, 1983) and Hodgkin's disease (Goodwin *et al.*, 1977) can produce significantly more $PGE_2$ than monocytes from normal individuals. Kunkel *et al.* (1986) reported that IL-1 was autoregulated through the induction of $PGE_2$. In this study, we examined the effects of indomethacin, which inhibits the synthesis of prostaglandins, on IL-1 production and found that IL-1 production in the control subjects and low stage patients was improved to the same degree, whereas it did not reach the control level in the high stage patients. This showed that the patients may have a different suppressor mechanism against IL-1 production independent of $PGE_2$. The monocyte-macrophage lineage has a variety of functions and plays an important role in the host defence mechanism against malignancy. Further studies on the role of monocytes in tumour progression should provide some insight into clinical immunotherapy.

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# Influence of Retinoids on Bladder Cancer Growth as Detected by Primary Tissue Culture

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Summary—The ability of the retinoid compounds, all-trans and 13-cis, to inhibit the growth of bladder tumour cells was investigated in primary tissue culture. A significant decrease in tumour growth was evident in 9 human bladder cancer patients. Since retinoid compounds are able to delay the progression or induction of tumours in primary tissue culture, their trial use as intravesical agents may be warranted.

Many primary human cancers arise in epithelial tissues which may depend upon retinoids for normal cellular differentiation. Since retinoids are involved in the induction or enhancement of cellular differentiation, they may also be able to prevent or reverse the process of carcinogenesis by modulation of the mechanism involved in differentiation (Moon *et al.*, 1983). The ability of retinoid compounds to inhibit or delay the appearance of human superficial bladder cancers (Alfthan *et al.*, 1983) and carcinogen-induced animal bladder cancers has been well documented (Lower and Kanarek, 1981). These effects of retinoids on tumour cells prompted us to study the ability of 13-cis and all-trans retinoic acid to inhibit the growth of human bladder cancer cells in primary tissue culture.

## Materials and Methods

Nine human bladder cancer specimens were obtained by cold cup biopsy through the cystoscope. Normal urothelium was surgically stripped from mesodermal tissues during open prostatectomy. None of the bladder cancer patients had been previously treated with intravesical chemotherapeutic agents. A chemically induced murine transitional cell carcinoma, N-[4-(5-nitro-2-furyl)-2-thiazolyl] (FANFT), maintained as a subcutaneous transplant in the C3H/He mouse, was also studied.

The bladder tumour grade/stage distribution is shown in the Table.

### *Enzymatic Disaggregation*

Surgical specimens were collected and placed into sterile tubes containing Dulbecco's modified Eagle's minimal essential medium (DME) containing 20% fetal calf serum. Tissue was placed in ice, brought immediately to the laboratory, minced in a mixture of 0.8% collagenase and 0.002% DNase in DME containing 20% calf serum and digested for 2 h at 37°C in a humidified atmosphere of 5% carbon dioxide/95% air. After 1 hour's digestion, mincing of tissue was repeated (Slocum *et al.*, 1981). The digested material was layered over 30% metrizamide in DME and centrifuged at 1000 × g for 20 min to remove damaged, non-viable cells and undigested material. Cells located at the interface of the 30% metrizamide were collected, washed 3 times in DME and plated in DME containing 10% fetal calf serum at a density of $1 \times 10^5/0.2$ ml in a 96-well microtitre plate. More than 95% of these cells excluded Trypan Blue.

**Table** Grade and Stage of Bladder Tumours

| *Grade* | *No.* | *Stage* | *No.* |
|---|---|---|---|
| I–II | 3 | T0–T1 | 5 |
| III–IV | 5 | T2–T4 | 3 |
| | | Tis | 1 |

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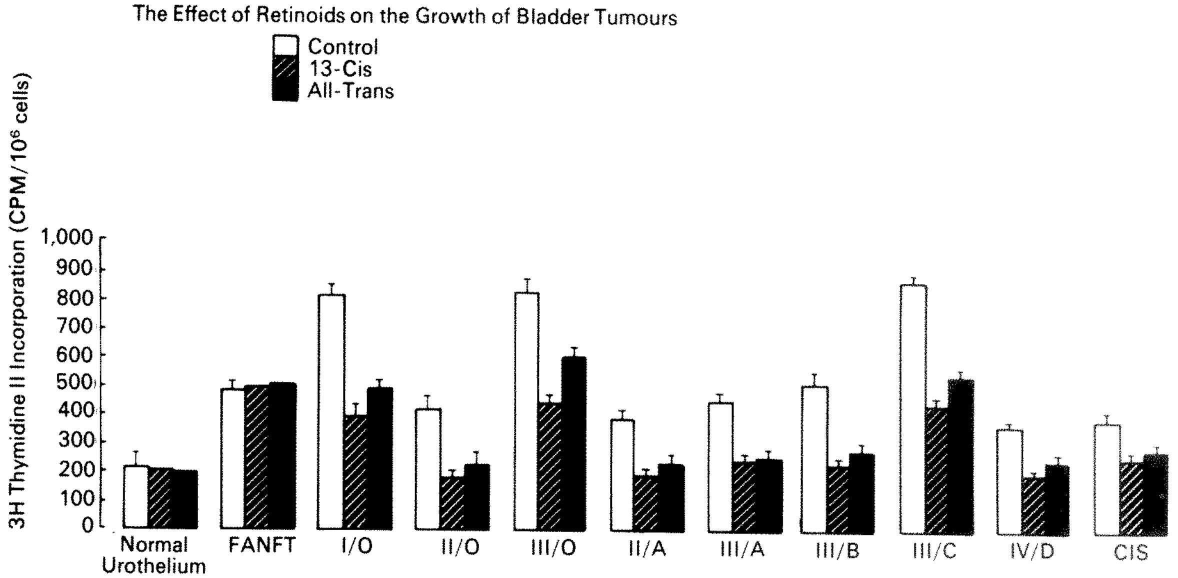

**Fig.** Results of $^{3}$H-thymidine incorporation in normal human urothelium, FANFT-induced murine TCC and human TCC after treatment with either 13-cis or all-trans retinoic acid.

Following disaggregation, 13-cis and all-trans retinoic acid (Hoffman-LaRoche) were added to each well at a final concentration of $10^{-6}$M. The solvent used for the retinoids as well as the control well was ethanol (1 ml/well). Cells remained in this medium for 4 days at 37°C; $2 \times 10^{4}$ CPM of tritiated thymidine (1 mCi/ml) in DME were added to each well and following 24 hour's incubation the cells were harvested, digested with NaOH and uptake of $^{3}$H-thymidine determined by scintillation counting. Each sample was tested in triplicate.

## Results

Neither the normal urothelium nor the FANFT tumour exhibited inhibition of cell growth as detected by incorporation of $^{3}$H-thymidine. However, all 9 human bladder cancers showed significant inhibition of cell growth by either 13-cis or all-trans retinoic acid treatment. This inhibition was not a result of direct cytotoxicity because neither cell debris nor detached cells were observed and cell viability remained over 90% (Fig.).

## Discussion

Bladder carcinogenesis is a multistep phenomenon during which discrete changes in the normal urothelial genome result in malignant clones. Attempts at inhibiting or delaying this dedifferentiation process by adjuvant agents have had varying results. Retinoids are known to be essential for proper differentiation of epithelial tissues by either reinforcing normal phenotypic expression or by preventing abnormal expression. The ability of the retinoid compounds, all-trans and 13-cis, to inhibit the growth of bladder tumour cells was investigated in primary tissue culture by measuring thymidine up-take. Primary tissue culture preparations of cold cup tumour biopsy specimens were treated with both 13-cis and all-trans retinoic acid. A significant decrease in tumour growth rate was evident, suggesting that the previously observed anti-tumour activity of retinoids *in vivo* is at least partly due to direct inhibition of cell proliferation. However, 13-cis and all-trans retinoic acid failed to inhibit *in vitro* growth of the FANFT-induced bladder carcinoma, suggesting that inhibition may be carcinogen—class specific as previously reported by Croft *et al.* (1981).

Since human bladder tumour growth was significantly inhibited *in vitro* by treatment with 13-cis and all-trans retinoic acid, further experimentation in the use of these agents as intravesical therapy is warranted.

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# Life with a Urostomy

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Summary—The quality of life of urostomy patients was assessed by direct interview. Specific problems, such as urine leakage, were documented and the size, site and quality of the stoma were assessed. The study included 41 patients; 83% noted an improvement in the quality of life since their urinary diversion and 90% were still able to work or continue to perform household duties. Urine leakage was the commonest problem and this was unrelated to the length of the stoma or the build of the patient. More important factors were the correct siting of the stoma and the avoidance of parastomal herniation. All patients emphasised the importance of the stoma therapist.

Urinary diversion using an ileal conduit was first described by Seiffert in 1935 and popularised by Bricker in 1950. Since then much has been written about the technical aspects of the operation but little attention has been paid to the practical problems faced by patients.

Recent reports suggest that both the practical problems and the psychological difficulties associated with a urostomy result in an impairment of the quality of life (Jones *et al.*, 1980; Hendry, 1982; Boyd *et al.*, 1987; Miyakawa and Yoshida, 1987; Mansson *et al.*, 1988). Despite progress in stoma care nursing and appliance manufacture, a personal paper suggested gross inadequacy in both of these fields (Benzies, 1986). Current trends favour urinary undiversion and the formation of continent stomas requiring intermittent self-catheterisation, but despite these technical advances it is still a matter of opinion as to whether these innovations represent an advance from a practical and psychological viewpoint (Ashken, 1987).

We assess the problems experienced by a group of urostomy patients and examine the importance of technical aspects such as the site and length of the stoma.

## Patients and Methods

At the time of this study there were 41 adult patients with urostomies under the care of the consultant urologists at the Royal Infirmary and Southmead Hospital, Bristol. Their names were obtained from the stomacare departments in each hospital. Only those patients who had undergone urinary diversion at least 6 months previously were included. No patient refused to take part in the study. The patients were interviewed and examined by one of the authors (D.J.C.). The interview took the form of a questionnaire asking about the type of appliance, its management and the quality of life since urinary diversion. The stoma was examined and its length measured. The site of the stoma was assessed as "good", "fair" or "poor", depending on its proximity to the umbilicus, bony landmarks, skin creases and surgical scars. The presence or absence of a parastomal hernia was noted.

## Results

The 41 patients included 20 men (age range 16–82 years, mean 52). The length of time since urinary diversion ranged from 6 months to 20 years (mean 5.9 years). The indications for the procedure are shown in Table 1.

Three types of appliance were used: 22 patients used the Squibb Surgicare System 2 (2-piece) and 5 used the Coloplast system (1-piece); 27 patients (66%) had tried more than 1 type of appliance, with 1 patient claiming to have used 12 different systems. The frequency of bag change is shown in the Figure. Those with 2-piece systems generally left

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**Table 1** Indications for Urinary Diversion

| | |
|---|---|
| Bladder cancer | 21 |
| Neurogenic bladder | 11 |
| Tuberculosis | 3 |
| Interstitial cystitis | 3 |
| Gynaecological malignancy | 2 |
| Ectopia vesicae | 1 |
| Total | 41 |

the base plate in place for a week before renewing it.

Five patients had experienced difficulty with supply: in 4 cases the manufacturer was blamed and in 1 case the fault lay with the local chemist.

In response to the question about their quality of life, 34 patients (83%) stated that it had improved since the urinary diversion; 5 (12%) stated that their quality of life was unchanged and 2 (5%) noted a deterioration.

Thirty-five patients (85%) were totally independent in the care of their stoma, and 6 needed help with bag changes from either their spouse or the district nurse.

Thirty-seven patients (90%) were still able to work if previously employed, or able to perform household duties; 37 patients (90%) claimed that the urostomy did not restrict their social life, whilst 4 stated that their social life was impaired.

The 16 men who had undergone cystectomy for bladder cancer were all impotent. Of the remainder, 10 had been sexually active prior to urinary diversion; 8 of these continued to enjoy a satisfactory sexual relationship but 2 were not sexually active as a direct result of their urostomy. One 55-year-old woman, who had undergone diversion for neuropathic bladder, abstained from intercourse because of dyspareunia. The other patient was a 39-year-old woman with urinary fistulae secondary to carcinoma of the cervix and subsequent radiotherapy. She had developed marital difficulties culminating in a divorce which she attributed, in part, to her urinary diversion. Twelve patients (29%) had difficulty during car journeys because of seat belts.

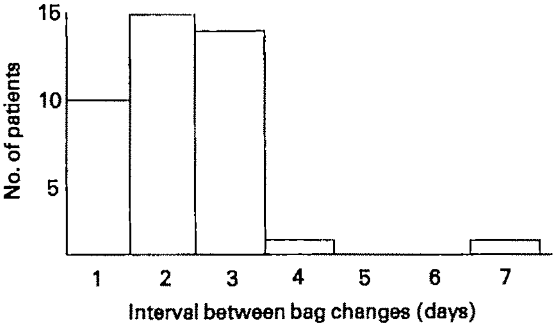

**Fig.** Interval between bag changes.

**Table 2** Urine Leakage and its Association with Patient Build and Length and Position of the Stoma

| | | *Leaks/week* | | |
|---|---|---|---|---|
| | | *None* | *<1* | *1–6* |
| Patient build | Thin | 2 | 1 | 3 |
| | Average | 8 | 8 | 4 |
| | Obese | 3 | 9 | 3 |
| Position of stoma | Poor | 0 | 0 | 3 |
| | Fair | 2 | 10 | 3 |
| | Good | 11 | 8 | 4 |
| Length of spout | <1 cm | 1 | 2 | 3 |
| | 1 cm | 7 | 10 | 4 |
| | 2 cm | 5 | 6 | 3 |

None of these differences was statistically significant.

**Table 3** Practical Problems Other than Urine Leakage

| | |
|---|---|
| Bleeding | 31 |
| Mucus secretion | 27 |
| Skin problems | 19 |
| Odour | 15 |
| Crust formation | 8 |

Urine leakage was the most important worry to many patients. Table 2 shows the frequency of leakage and its relation to both the build of the patient and the length and position of the stoma. Thirteen patients (32%) had never experienced a leak but most of the remainder (18 patients, 44%) leaked at a frequency of less than once per week; 4 patients (10%) had a parastomal hernia and all of these leaked. Of the 28 patients who experienced urine leakage, 12 blamed "appliance failure", such as leakage from a seam or from around the tap. The other 16 stated that leakage occurred from the junction of the adhesive base-plate and the skin.

Other practical problems are listed in Table 3. Minor bleeding following trauma to the stoma was very common. It always stopped spontaneously. Mucus secretion from the conduit also occurred in many cases but rarely blocked the stoma or caused problems with bag emptying. Skin problems were temporary and always responded to the use of barrier creams or changing the base-plate. None of the patients was concerned about an unpleasant odour arising from the appliance.

All patients, without exception, considered the stoma therapist to be the most important person in the management of the appliance and in the treatment of these practical problems.

## Discussion

The research described in this study was prompted by a personal report by a urostomy patient (Benzies, 1986). He was dissatisfied both with the appliance and with the counselling advice he had received. The patients reviewed in Bristol, however, seemed generally satisfied, with 83% reporting an overall improvement in their quality of life. This is a somewhat surprisingly high proportion. Whilst at one end of the spectrum, patients with incontinence and gynaecological fistulae would clearly be grateful for a diversion, it is difficult to believe that many patients with bladder cancer would be similarly satisfied (Malone *et al.*, 1985). This may reflect local policies.

The patients in this survey compare favourably with those in a similar study by Jones *et al.* (1980). In the Bristol series a higher percentage of patients returned to work and very few needed to restrict their social activities. In addition, sexual problems were less common.

The major practical problem remains that of urine leakage. Appliance failure accounted for leakage in nearly half of the 28 cases and was remedied by collecting a new batch of appliances. This suggests that product quality control could be improved. Neither the length of the stoma nor the build of the patient affected the frequency of urine leakage. The more important factors appear to be correct siting of the stoma together with careful technique to avoid parastomal herniation. These factors have been emphasised by Witherington *et al.* (1977).

Skin reactions are usually temporary and may be cured by simple nursing measures. This problem has been scientifically evaluated and is one of the reasons for the development of the new generation of non-adhesive urostomy appliances (Bergman *et al.*, 1982; Duffy and Lange, 1985).

The role of the stoma therapist in the long-term management of these patients cannot be overemphasised. All patients stated that the stoma therapist was the single most helpful person in the management of the urostomy. They found hospital doctors, general practitioners and district nurses to be unhelpful in this respect.

In summary, we were surprised to learn how many patients were happy with their urinary diversion.

The surgeon must maintain careful selection of patients and take care in the technical aspects of construction of the stoma, especially with regard to its position. The manufacturers must improve quality control and, together with the pharmacists, must maintain a steady supply of appliances. Finally, every urological centre must have access to the services of a trained stoma therapist.

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# Prostatic Stenting for Outflow Obstruction

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Summary—A series of 30 patients with outflow obstruction underwent treatment with prostatic stents. Most had retention of urine and were unfit for conventional surgery. The prostatic stent was readily inserted under local anaesthesia and successfully relieved obstruction in 80% of patients with acute retention. Minor problems were common but there were few major complications.

Modern anaesthetic techniques enable us to perform transurethral surgery on the majority of patients who require prostatectomy. Nevertheless, there remains a small group of very high risk patients who are excluded from surgery and who are managed with long-term catheters. Drug treatment with selective alpha-adrenergic blocking agents has a very limited place in these patients. A mechanical approach using a prostatic stent is a more promising alternative to a long-term catheter. A prostatic stent, or partial catheter, was described by Fabian (1980). Various modifications have since been reported and results have been encouraging, although the technique of introduction has sometimes proved difficult (Langkopf *et al.*, 1981; Fabian, 1984). We have used a modified spiral developed in Denmark under the name PROSTAKATH.

## Patients and Methods

The prostatic stent (Fig. 1) is a gold-plated, spring-like spiral with an outside diameter of 21 F. It is tapered proximally to facilitate introduction into the prostatic cavity, where the main body of the spiral lies. There is a narrow neck which passes through the sphincter area and a distal coil which sits in the bulbar urethra and allows adjustment or removal of the stent. It is available in 5 lengths ranging from 45 to 85 mm. The gold plating is said to reduce encrustation and bacterial growth.

The present study involved 30 patients treated between July 1988 and May 1989. The age range was 65 to 93 years (mean 80). Twenty-two patients had retention of urine; all were unfit for surgery and 10 had evidence of chronic retention. Of those with obstructive symptoms alone, 4 were unfit for surgery. In addition, 3 patients who were awaiting prostatic surgery, and 1 with equivocal outflow obstruction, were offered prostatic stents. There were no medical contraindications to surgery in these 4 patients (Table 1). The associated medical problems are listed in Table 2. The risk category, using the American Society of Anesthesiology's fitness grading, is shown in Table 3.

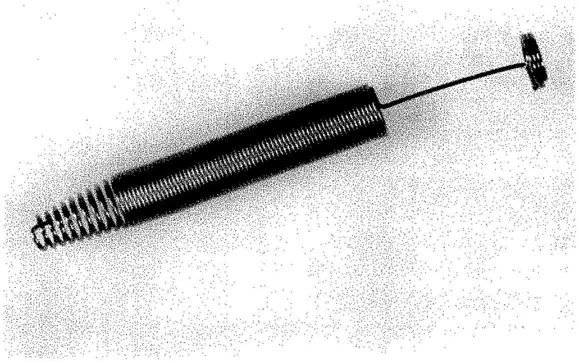

**Fig. 1** The PROSTAKATH prostatic stent.

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

**Table 1** Prostakath Trial: Presenting Features

| | *No. of patients* |
|---|---|
| Retention | 22 |
| Acute | 12 |
| Chronic | 10 |
| Obstructive symptoms | 8 |
| Unfit for surgery | 4 |
| Awaiting TUR | 4 |

**Table 2** Associated Medical Problems

| | *No. of patients* |
|---|---|
| Cardiac | |
| LVF | 3 |
| Recent MI | 4 |
| Other | 1 |
| Recent CVA | 4 |
| Respiratory problems | 1 |
| Malignant disease | 3 |
| Bronchus | |
| Pharynx | |
| Kidney | |
| General frailty and debility | 10 |
| | 26/30 |

**Table 3** American Society of Anesthesiology: Fitness Grading

| *ASA category* | *No. of patients* |
|---|---|
| 1. Healthy | 3 |
| 2. Mild systemic disease | 1 |
| 3. Severe systemic disease—functional limitation | 11 |
| 4. Severe systemic disease—threat to life | 15 |
| 5. Moribund | 0 |

Prior to treatment all patients had urine samples cultured, blood creatinine, urea and electrolyte estimations and a plain X-ray and ultrasound of the urinary tract. Flow rates were obtained in patients not in retention.

Insertion was performed under local urethral instillation of anaesthetic, with the patient in the lithotomy position.

In addition, sedation with midazolam (2.5–5 mg) was usually given. All patients received a prophylactic dose of intravenous gentamicin. Using a 17 F Miller cystoscope, the bladder was first checked and the length of the prostatic cavity from bladder neck to veru measured under direct vision to allow a stent of suitable length to be selected. A ureteric catheter (6 or 7 F) was inserted into the bladder to act as a guide.

The PROSTAKATH is mounted on an integral catheter for introduction and is passed over the ureteric catheter until the tip is judged to be in the bladder as indicated by urine appearing in the catheter. The ureteric catheter is withdrawn, the introducing catheter disconnected and removed and the stent left in place. The distal position of the stent is checked endoscopically.

Subsequently we found it more satisfactory to dispense with the catheter mount and to introduce the stent over the ureteric catheter guide under direct vision until the tail was seen sitting in the bulbar urethra. Adjustments to the position can be made with grasping forceps.

Patients were allowed to void as soon as they wished and the position of the stent checked the following day by plain X-ray.

Patients who went into retention, or who had haematuria, had a suprapubic catheter inserted under local anaesthesia as the stent does not allow a urethral catheter to be passed.

Patients were followed up as out-patients at 4 weeks, and subsequently 3-monthly. Urine samples were cultured and where possible flow rates obtained and ultrasound residual estimated.

## Results

### *Retention Group (Table 4)*

Of the 22 patients in this group, voiding was established in 18 (82%). Four patients who were unable to void had suprapubic catheters inserted. Of these, 1 patient who was terminally ill with advanced carcinoma of the bronchus died the day after the procedure. The second patient had the stent removed and a long-term catheter inserted as the risks of surgery were considered too great. The third and fourth patients had their stents removed and underwent transurethral prostatectomy under spinal anaesthesia. One of these, with chronic retention, remained incontinent after surgery and had a long-term catheter inserted. Satisfactory voiding was established in the other patient.

**Table 4** Initial Results

| *Retention patients* | *No.* | % |
|---|---|---|
| Voiding established | 18/22 | 82 |
| Acute retention | 11/12 | 92 |
| Chronic retention | 7/10 | 70 |

Only 1 patient in the acute retention group failed to void.

*Subsequent Outcome*

A useful result was achieved in 10 of 19 patients (52%) (Table 5). Most of the unsatisfactory results occurred in patients with chronic retention; incontinence related to inadequate voiding being the main problem. These patients either had the stent removed and a urethral catheter placed or, for 1 patient, a suprapubic catheter was inserted (Table 6).

After insertion of the stent, flow rates in the retention group were measured in 8 patients and are shown in Table 7. Of the patients with outflow symptoms, but not in retention, only 4 (50%) showed subjective improvement. Flow rates were only marginally better; 3 of the 4 patients with improvement were considered unfit for prostatic surgery (Table 8).

**Table 5** Subsequent Results

| *Retention patients* | *No.* | % |
|---|---|---|
| Useful outcome | 10/19 | 52 |
| Acute retention | 7/9 | 78 |
| Chronic retention | 3/10 | 30 |

**Table 6** Chronic Retention Failures (7/10)

| *Reason for failure* | *Outcome* |
|---|---|
| Incontinent | Stent removed/catheter |
| Incontinent | Stent removed/catheter |
| Incontinent | Suprapubic catheter |
| Died 24 h later | |
| Incontinent | Stent removed/catheter |
| Failed to void | Stent removed/catheter |
| Failed to void | TUR—successful |

**Table 7** Flow Rates following Stent Insertion in 8 Patients

| | |
|---|---|
| Peak flow (range) | 8.3–23.8 ml/s |
| Mean | 14.5 ml/s |

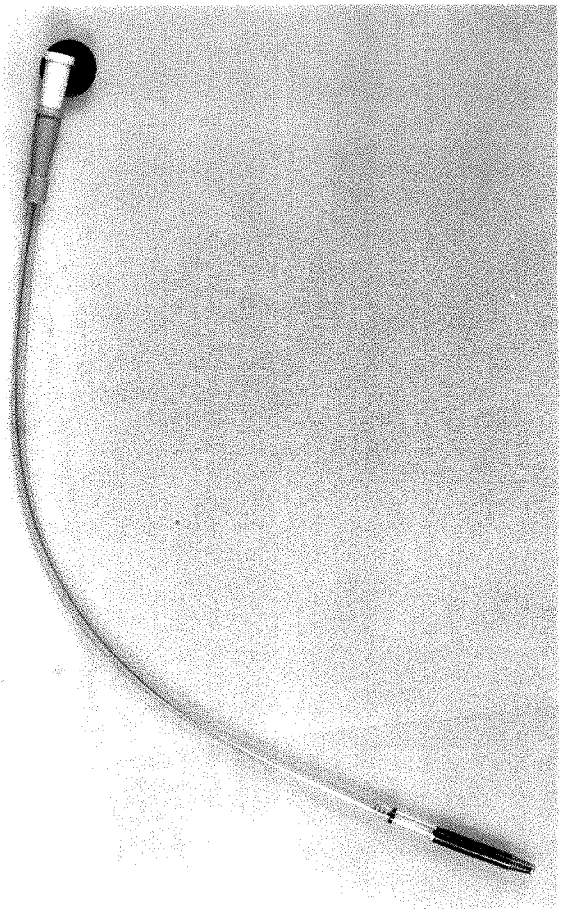

**Fig. 2** The prostatic stent on integral catheter introducer.

The duration of hospital stay was variable. Patients who had no problems were discharged within 48 h, but others were in hospital for much longer, with medical and social factors contributing to this.

*Complications (Table 9)*

Minor problems following insertion of the stent were common, with early adjustments to its position being necessary in 11 patients. With increasing experience this is now a less frequent occurrence.

Haematuria from prostatic bleeding leading to stent blockage and the need for a suprapubic

**Table 8** Results in Prostatic Symptom Group

| | *No.* | % |
|---|---|---|
| Symptoms improved | 4/8 | 50 |
| Unfit for surgery | 3/4 | 75 |
| Elective | 1/4 | 25 |

**Table 9** PROSTAKATH Complications

| | *No.* |
|---|---|
| Stent adjustment | 11 |
| Haematuria (requiring suprapubic catheter) | 4 |
| Incontinence: nocturnal only | 2 |
| Failed insertion | 1 |
| Stent displacement to bladder | 1 |
| Urinary infection | 1 |
| Stricture | 1 |

catheter occurred in 4 patients; 2 had persistent nocturnal enuresis despite good bladder emptying and good bladder control in the daytime.

There were technical difficulties in inserting the stent in 2 patients. In 1 case the anterior urethra was too tight to accept the stent and although this was readily overcome by dilatation, the stent failed to negotiate the membranous urethra and the procedure was abandoned. Since the patient was from the elective prostatectomy waiting list, he underwent transurethral resection without further delay. In a second patient there was difficulty in placing the stent and the procedure was abandoned because of prostatic bleeding. However, successful insertion was carried out a week later.

Since using the modified technique of introduction under direct vision, we have not encountered any problems with insertion.

Symptomatic urinary infection occurred in only 1 patient. He was an insulin-dependent diabetic who, although voiding successfully following insertion of the stent, had residual urine and developed a severe urinary infection 4 months after insertion. His infection cleared with antibiotics following removal of the stent and placement of a long-term catheter.

One patient developed a urethral stricture 5 months after stent insertion. He had had no problems for 3 months and then developed urinary incontinence associated with a deterioration in his physical and mental condition. At endoscopy to remove the stent the bulbar coil was found buried in a short, soft stricture. This was readily divided by visual urethrotomy, the stent removed, and an indwelling catheter inserted.

In a patient with chronic retention and very little prostatic tissue, who failed to void, the stent was shown by X-ray to be in the bladder. He was extremely frail and, without removing the stent from the bladder, a urethral catheter was inserted. He died shortly afterwards from his medical condition.

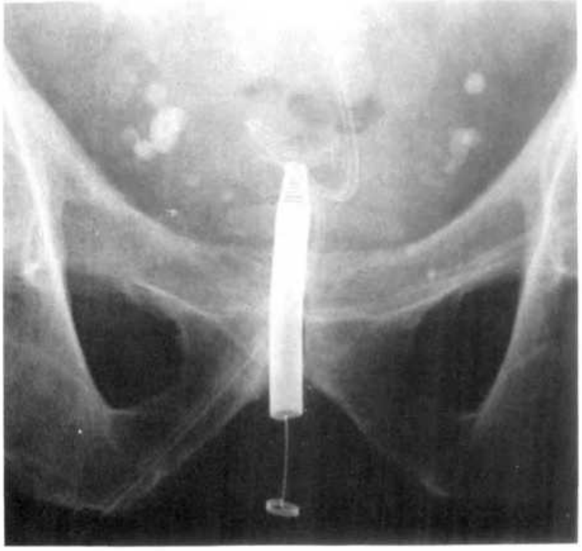

**Fig. 3** Plain X-ray showing PROSTAKATH in place and suprapubic catheter.

*Mortality*

There was no mortality directly related to the procedure but 4 patients have died since stent insertion: 2 with cardiac problems and 2 from advanced malignant disease.

## Discussion

We have found the PROSTAKATH stent relatively easy to insert and now favour doing so under direct vision. Others (Nordling *et al.*, 1988; Langemeyer *et al.*, 1988, unpublished observations) have successfully used the mounted catheter introduction technique controlled by ultrasound.

Adjustment of the stent's position, using grasping forceps inserted down the instrument channel of the cystoscope, is readily achieved and a similar technique has been used for removal. To reduce the risk of urethral trauma from the stent during removal it is possible to perform the procedure through an outer catheterising sheath of a large resectoscope.

Patients have tolerated the stent well; any local discomfort has occurred within the first few days and has been minimal, but no patient has been sufficiently fit to ride a bicycle.

Although the overall success rate is just over 50%, the majority of failures have been in patients with chronic retention and we now feel that this group is generally unsuitable for prostatic stenting. A poorly functioning detrusor may be unable to generate sufficient pressure to overcome the resistance of the prostatic spiral. We performed urodynamic studies via a suprapubic catheter in 2 patients who failed to void following insertion of the stent and found that both had acontractile detrusors. With careful selection of patients, good results can be expected from a prostatic stent and we recommend its use in patients with acute retention of urine where the risks of transurethral surgery are considered too high, before resorting to a long-term catheter.

Encrustation of the stent may be a problem in patients who survive long enough (Langemeyer, 1988, unpublished observations), although we have not yet encountered this. Stent replacement should be possible.

It must be remembered that with a stent in place, urethral catheterisation or cystoscopy cannot be performed.

The position of the stent is maintained by being gripped by the prostatic urethra. In some patients the configuration or length of the prostatic cavity was insufficient to hold the stent firmly, leading to stent migration, although only in 1 of our patients did the stent become displaced into the bladder. However, the stent's fixed diameter is a limiting factor and sometimes it may be too large to negotiate the urethra, yet too small to maintain its position in the prostatic cavity. It may also present too much resistance to flow to allow voiding at low detrusor pressures. An expandable stent, similar to that being used for urethral strictures, would overcome these difficulties (Milroy *et al.*, 1989). However, this type of mesh stent becomes epithelialised and cannot readily be removed. There seems scope for further development in the design of prostatic stents.

The ability to remove the PROSTAKATH stent makes it suitable for temporary use in patients who are unable to undergo immediate prostatectomy, either on medical grounds or because of domestic circumstances or waiting list delays. It seems less likely to be of significant benefit to patients awaiting elective prostatectomy unless their outflow symptoms are very marked.

We conclude that prostatic stent insertion can readily be achieved under local anaesthesia and sedation, using standard urological instruments. The procedure takes only a few minutes and is suitable for ASA Grade 4 patients.

The stent relieves outflow obstruction in acute retention, is well tolerated and a preferable alternative to a long-term catheter.

## Acknowledgements

Advice on the anaesthetic assessment and sedation of the patients was given by Dr A. C. L. Fraser, Consultant Anaesthetist. We are grateful to Mr M. G. Royle and Mr M. S. Fletcher for their co-operation.

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# A New Self-retaining Intraurethral Device

## An Alternative to an Indwelling Catheter in Patients with Urinary Retention due to Infravesical Obstruction

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Summary—A new self-retaining intraurethral catheter, designed as an alternative to an indwelling catheter, has been used in 14 patients. It was left in place for 2 to 18 weeks; 11 of the 14 patients were able to void freely, were continent and had neither residual urine nor urinary tract infection. This device may be used instead of an indwelling Foley catheter in patients with retention due to infravesical obstruction and may be an alternative to prostatectomy in patients who are at high risk for surgery.

The main reason for leaving an indwelling catheter in place for a prolonged period of time is to relieve urinary retention, most often due to infravesical prostatic obstruction. Because of the disadvantages and possible complications of an indwelling catheter, an intraurethral prosthesis has been designed and inserted into the posterior urethra as an alternative to an indwelling catheter in patients with benign prostatic hyperplasia. Our experience with this device in 14 patients is reported.

### Patients and methods

The newly developed intraurethral catheter (IUC) resembles a double Malecot 16 F polyurethane catheter (Puroflex—Urosoft, Angiomed, West Germany), 45, 55 and 60 mm long (Fig. 1). It is positioned in the bladder neck and prostatic urethra through a cystoscope sheath (22F) (Fig. 2).

The patient is placed in the lithotomy position. Through the indwelling catheter, 150 ml of saline are infused into the bladder; the catheter is then removed and the urethra lubricated with 10 ml lignocaine jelly. A penile clamp, obstructing the distal urethra, is left for 10 min. The cystoscope sheath containing the IUC in its curved end is then introduced into the bladder. The previously infused saline then flows out via the cystoscope. The cystoscope is drawn slightly into the bladder neck when the fluid has ceased to flow from the cystoscope sheath and the IUC is expelled by the obturator of the cystoscope. The cystoscope sheath, together with the obturator, is removed from the urethra. The distal end of the IUC should be 1 cm distal to the verumontanum; this is verified by urethroscopy immediately after insertion of the IUC. The device may be pulled distally by the

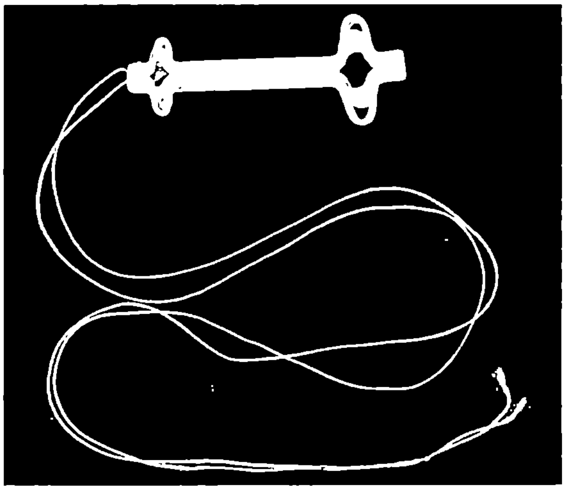

**Fig. 1** The intraurethral catheter.

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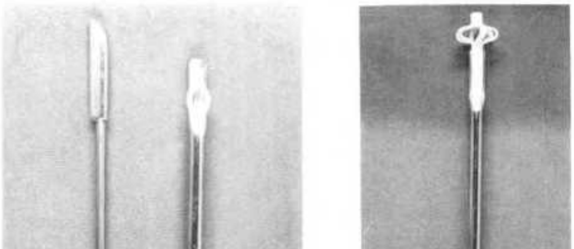

**Fig. 2** Insertion of the IUC through the cystoscope sheath. (A) Cystoscope containing the IUC. (B) Intraurethral catheter expelled from the cystoscope sheath by the obturator.

suture attached to its end or pushed upwards by the endoscope. The length of the prostatic urethra should be measured endoscopically or by ultasound, to enable the appropriate IUC to be chosen and inserted.

A non-resorbable multifilament nylon/silk 0.20 mm suture, connected to the distal end of the IUC, remains in the urethra and emerges from it. If necessary, the intraurethral catheter may be easily removed by pulling the thread, after the urethra has been lubricated by lignocaine jelly.

If the patient is able to void freely and is continent, the thread may be cut and shortened so that it is left in the navicular part of the urethra. If required, the nylon/silk suture may be grasped by biopsy forceps and the IUC removed after lubrication of the urethra.

Antibiotic therapy, according to urine culture, began 24 h before insertion of the IUC and continued for 5 to 7 days. The patients were followed up closely and questioned twice weekly regarding frequency and urgency of micturition, and continence during both day and night.

Urine cultures were taken weekly and ultrasound (to measure residual urine) was performed twice weekly during the first 2 weeks. In 6 patients, cystourethrography was performed 5 to 7 days after insertion of the IUC. Uroflows were obtained in 11 patients.

## Results

The intraurethral catheter was inserted in a non-consecutive series of 14 patients with indwelling catheters (in place from 3 weeks to 18 months) for urinary retention due to benign prostatic hyperplasia. The patients' ages ranged from 54 to 78 years. Details of the patients and the reasons for postponing surgery are given in the Table.

The IUCs were 45 mm long in 8 patients and 55 mm in the other 6. All patients were able to void after insertion of the IUC and were continent. In 11 patients the intraurethral catheter was left in place for 2 to 18 weeks.

In 2 patients the IUC was removed after 2 and 3 days because of severe frequency, poor stream and residual urine (250–320 ml). In the third patient the IUC was removed 6 h after insertion because of clot retention.

**Table** Details of Patients with Urinary Retention due to Benign Prostatic Hyperplasia

| *Patient No.* | *Age (years)* | *Clinical details** | *Duration of indwelling catheter (weeks)* | *Duration of IUC (weeks)* |
|---|---|---|---|---|
| 1 | 54 | MI | 5 | 2 |
| 2 | 65 | MI | 5 | 2 |
| 3 | 69 | MI | 7 | 2 |
| 4 | 73 | Severe heart failure | 26 | 2 |
| 5 | 69 | Awaiting surgery | 7 | 2 |
| 6 | 73 | CVA | 7 | 3 |
| 7 | 76 | CVA | 11 | 4 |
| 8 | 69 | CVA | 9 | 7 |
| 9 | 59 | Severe heart failure | 22 | 0 (2 days) |
| 10 | | Awaiting surgery | 6 | 0 (3 days) |
| 11 | 58 | MI | 3 | 8 |
| 12 | 59 | Awaiting surgery | 3 | 18 |
| 13 | 61 | MI after cardiac surgery | 17 months | 9 |
| 14 | 78 | MI | 8 | 0 (clot retention) |

* Less than 4 months after myocardial infarction (MI) or cerebrovascular accident (CVA).

The main complaint of the 11 patients who had retained the IUC for several weeks was frequency of micturition, with voiding intervals of 1.5 to 3.5 h. Some discomfort during voiding (burning sensation and urgency) disappeared 24 to 48 h after the IUC had been inserted; 3 patients had nocturia 3 to 4 times and 8 patients voided once or twice during the night. No patient developed clinically evident urinary tract infection, including the patient who had had the IUC for 18 weeks. All but 3 patients had negative urine cultures by the end of the first week. Voiding cystourethrography or ultrasound showed satisfactory voiding with no residual urine (Fig. 3). On mictiography, performed in 11 patients, maximum flow rates were 8.5 to 12.5 ml/s (mean 10).

## Discussion

Urethral catheters have been designed to serve several purposes: to relieve urinary retention, to test residual urine, to obtain urine directly from the bladder for diagnostic purposes, and for bladder lavage, instillations or other therapeutic reasons. However, a catheter is no longer needed either for testing residual urine or to obtain urine directly from the bladder.

The use of a catheter for therapeutic purposes, such as bladder instillation, remains essential, but in such cases a catheter is inserted for a short period of time, is removed shortly afterwards and the patient suffers relatively little discomfort. The same may be said for the use of a catheter after bladder or prostatic surgery.

The main reason for leaving catheters indwelling for weeks or months is to relieve urinary retention, most often due to infravesical prostatic obstruction.

In many instances an indwelling catheter has to be left in place for an extended period of time either because the patient is unfit for surgery, or because his condition requires that surgery be postponed, as was the case with most of the patients in this series. Unfortunately, in many countries there is a waiting list of patients for prostatectomy, many of whom must endure an indwelling catheter for weeks or even months.

An indwelling catheter is not only a common cause of urinary tract infection, urethral discharge,

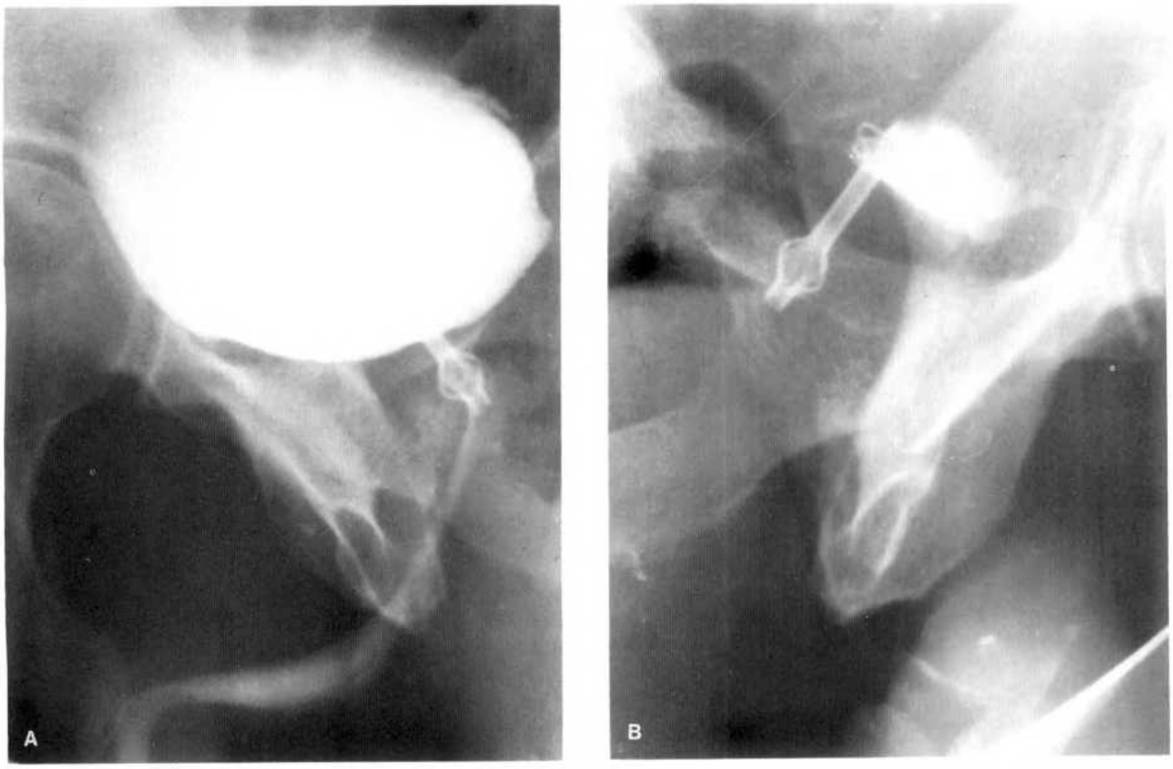

**Fig. 3** (A) Voiding cystourethrography of a 59-year-old man who had had the IUC for 18 weeks. (B) Note complete emptying of the bladder.

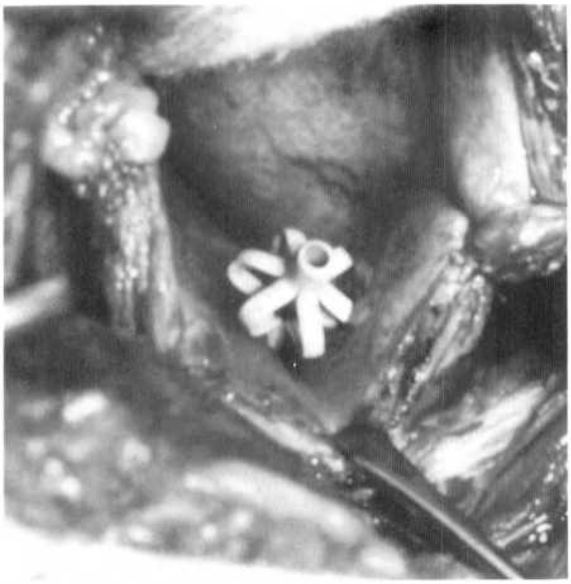

**Fig. 4** Intraoperative view of the intraurethral catheter during transvesical prostatectomy. The upper part of the IUC is located in the bladder neck.

possible urethral stricture and many other complications, but is also a serious psychological problem. Most men with an indwelling catheter feel they lose dignity, are unable to perform sexually and are often unable to continue their routine way of life. In addition, they have to suffer local discomfort caused by the catheter irritating the entire length of the urethra, although only a few centimetres are needed to overcome the obstruction.

Only 1 alternative to an indwelling catheter has so far been assessed. This is an iron, gold-coated spiral (Fabian, 1984). The results reported by Langemeyer (1988) and Nordling (1988) (unpublished observations), in a series of 17 and 13 patients respectively, were promising.

The intraurethral catheter now described is a simpler and more physiological prosthesis. It is easier to insert into the prostatic urethra, easier to remove and is less costly than the gold-coated spiral.

The results have shown that for a period of several weeks, when the IUC was left as an internal stent, 11 of 14 patients were able to void, had no residual urine, and all were continent. In spite of some frequency, all patients preferred the IUC to the indwelling catheter. Although 3 patients were unable to void satisfactorily after insertion of the IUC, it is possible that reinsertion after several days might have been successful. The fact that the patients were continent is not surprising, as it is well known that the distal continence mechanism is sufficient to ensure continence.

In 2 cases the IUC was removed during open prostatectomy and no damage was observed in the urethra or bladder neck, or any evidence of encrustation. An intraoperative view of the IUC is shown in Figure 4.

Additional experience in placement of the IUC and evaluation of the role of the prostate in interference with the bladder neck opening are needed in order to improve the pattern of voiding and thus reduce frequency in some patients.

Our preliminary experience leads us to suggest that this new intraurethral catheter may avoid the need for an indwelling catheter in many patients with urinary retention due to benign prostatic hyperplasia; it may also be of help to patients who are at high risk for surgery. In such patients, the IUC should be changed every 4 to 6 months.

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# Local Hyperthermia of the Prostate Gland for the Treatment of Benign Prostatic Hypertrophy and Urinary Retention

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Summary—Local hyperthermia of the prostate was used to treat 72 patients who had an indwelling catheter because of urinary retention caused by benign prostatic hypertrophy. One month after completion of treatment 50% of patients were able to dispense with the catheter and 1 year later 40% remained catheter-free. The best results were achieved in patients who underwent 6 to 10 treatment sessions in conjunction with cyproterone acetate 50 mg *tid* administered during the treatment period only.

The treatment of benign prostatic hypertrophy (BPH) by local hyperthermia is a recent development. The mechanism of action and the biological processes are not completely understood but preliminary results are encouraging (Servadio *et al.*, 1986, 1987; Lindner *et al.*, 1987).

It is not possible to obtain a full objective assessment of the complaints and symptoms in patients with BPH and evaluation of the results of treatment is therefore difficult. We have tried to minimise this problem by adhering to a very strict protocol. Following animal studies and a phase I study (Leib *et al.*, 1986; Servadio *et al.*, 1986), we established the safety of thermal treatment of the prostate gland using the Prostathermer. We have now carried out a prospective phase II study in 3 medical centres in order to establish the efficacy of this treatment.

## Patients and Methods

For local hyperthermia of the prostate we used the Prostatherma (TM) system model 99-D as described by Lindner *et al.* (1987). It consists of a microwave generator operating at 915 MHz, an applicator, a water cooling system, temperature probes and an IBM PC-XT type computer. The applicator is introduced into the rectum and positioned at the level of the prostate.

The thermocouples are located on the applicator and housed in a specially adapted 18 F urinary catheter which is inserted into the bladder before treatment. The maximal prostatic temperature is calculated throughout treatment and is based on temperatures measured in the rectum and prostatic urethra.

The study group comprised 72 men (age range 58–92 years, mean 76.7); all had an indwelling catheter because of bladder outlet obstruction caused by BPH. Pre-treatment evaluation consisted of a medical history, physical examination, intravenous urography, transrectal ultrasound of the prostate, proctoscopy and laboratory tests including SMA 12, CBC and urine analysis. An objective assessment of the results was achieved by using a scoring system which took account of peak urine flow and residual urine (Table 1).

All patients were treated with phenoxybenzamine hydrochloride 10 mg/day for 5 days, after which time the catheter was removed. Uroflowmetry was performed and residual volumes of urine measured. If the score was less than 15 points the catheter was reinserted. If the score was 15 points or more the patient remained without a catheter

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**Table 1** Objective Scoring Table

*Urinary flow rate*

| *Max flow rate (ml/s)* | *Volume voided* 0–50 | *51–100* | *101–150* | *170–200* | *>200* |
|---|---|---|---|---|---|
| 20 | 9 | 9 | 9 | 9 | 9 |
| 18–19.9 | 9 | 9 | 9 | 8.5 | 8 |
| 16–17.9 | 9 | 9 | 9 | 8 | 7.5 |
| 14–15.9 | 9 | 8.5 | 8 | 7.5 | 7 |
| 12–13.9 | 8.5 | 8 | 7.5 | 7 | 6.5 |
| 10–11.9 | 7.5 | 7 | 6.5 | 6 | 5.5 |
| 8–9.9 | 6.5 | 6 | 5.5 | 5 | 4.5 |

*Residual urine rate*

| *Residual urine volume (ml)* | *Score* |
|---|---|
| 0–50 | 5 |
| 51–100 | 4 |
| 101–150 | 3 |
| 151–200 | 2 |
| >200 | 1 |

Total objective score = Urinary flow rate score × Residual urine rate score.

**Table 2** Details of Patients

| | *Group 1* | *Group 2* | *Group 3* | *Group 4* |
|---|---|---|---|---|
| Mean age (years) | 77.6±7.1 | 76.7±8.3 | 73.7±7.4 | 73.8±7.6 |
| Mean peak flow rate (ml/min) | 8.3±4.1 | 5.4±4.9 | 5.8±1.9 | 6.8±5.0 |
| Mean residual volume (ml) | 245 | 314 | 222 | 245 |
| Mean objective score rate | 10.6 | 8.4 | 14.2 | 14 |

and the assessment was repeated 1 week later. Patients were included in the study only after completion of this protocol. A similar evaluation was made when treatment was completed and every 3 months during follow-up.

Treatment was administered on an out-patient basis using local anaesthesia for insertion of the urethral catheter. The prostate was heated to 42±1.5°C during each treatment session, which lasted for 1 h. Patients were assigned randomly to one of the following groups:

Group 1. Low dose treatment: 3 to 5 sessions.
Group 2. Low dose treatment plus cyproterone acetate 50 mg *tid* during the treatment period only.
Group 3. High dose treatment: 6 to 10 sessions.
Group 4. High dose treatment plus cyproterone acetate 50 mg *tid* during the treatment period only.

The patients were of comparable age and degree of prostatic outflow obstruction (Table 2).

## Results

At the first follow-up, 1 month after completion of treatment, 36 patients (50%) no longer needed a catheter. One year after treatment 29 patients (40%) were still without a catheter and required no further treatment. Results showed that the success rate was dose-dependent. Of 27 patients receiving low dose therapy, 9 (33%) were catheter-free and of 45 patients in the high dose group, 27 (60%) no longer required a catheter. This was statistically significant ($P<0.01$ in a 2-tailed test). In group 1, 5 of 12 patients (41%) stopped using a catheter and in group 2, 4 of 15 patients (27%) were catheter-free. The difference did not reach statistical significance and it cannot therefore be concluded that there are any adverse effects from the medication and the low dose treatment.

In group 3, 13 of 26 patients (50%) dispensed with a catheter and in group 4, 14 of 19 patients (74%) were catheter-free. This was statistically significant ($P<0.04$ in a 2-tailed test).

A total of 104 patients were randomised. Twelve failed to complete all treatment sessions—4 because of unrelated death or disease, 4 because of discomfort related to the treatment and 4 because of complications associated with the treatment. Twenty patients were excluded because of infringements of protocol (mainly discrepancies in thermal dose calculations). The results were analysed only for the 72 evaluable patients but the complications were assessed for the whole group. Fever exceeding 38°C was recorded in 10 patients, rectal pain in 12, diarrhoea in 3 and haematuria in 11. Four patients were hospitalised (2 with severe haematuria, 1 with pain and 1 with bacteraemia).

## Discussion

The standard treatment for urinary tract obstruction caused by BPH is surgery. Although the overall mortality rate is less than 1%, in high risk groups it remains substantial. Morbidity is not well documented, but early complications (bleeding, infection, cardiopulmonary problems) and late complications (urethral stricture, bladder neck stenosis, impotence, incontinence) are well known. Efforts have continually been made to find a non-surgical form of treatment.

This study continues the work of Servadio *et al.* (1986) on the use of hyperthermia in the treatment of BPH. Although the procedure cannot be defined as non-invasive, it is non-surgical and invasion is minimal.

For ethical reasons no sham procedure was included in the protocol. By using many treatment arms, both in this protocol and in another one for uncatheterised BPH patients, we were able to show that the results are dose-dependent and hence not a placebo effect.

The best results were achieved in patients treated for 6 to 10 h in conjunction with cyproterone acetate 150 mg/day for the duration of the treatment period; 74% of patients in this group no longer needed a catheter. Scott and Wade (1969) reported good results when BPH was treated with cyproterone acetate 50 mg/day. This was confirmed by Ekman *et al.* (1981) in a controlled study. We therefore used cyproterone acetate as an adjuvant in 2 groups in order to assess any synergistic effect. Better definition of a favourable group of patients, based on prostatic size and configuration and the patient's age, will probably lead to improved results.

Our results suggest that hyperthermia is a viable alternative to surgery in patients with an indwelling catheter. This is certainly true in cases where surgery is absolutely contraindicated, *e.g.* recent myocardial infarction or cerebrovascular accident, and in more equivocal cases such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled hypertension, diabetes mellitus, etc. It is not yet possible to say whether this form of treatment is merely palliative or whether it will produce a permanent cure.

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# Sperm Motility, Velocity and Migration

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Summary—Four different methods for evaluating sperm motility were analysed for experimental error: subjective assessment of a wet film preparation, sperm velocity measured by time-lapse photography, sperm velocity measured by computer analysis and sperm migration across a nucleopore membrane.

Subjective assessment of motility was found to be inaccurate, within single observer and between 2 observers.

Both methods of measuring mean sperm velocity were accurate, particularly that using the computer analysis system; a high technical failure rate was found using time-lapse photography. Sperm migration across a nucleopore membrane was found to be highly inaccurate.

Two groups were then analysed for the predictive value of these tests (excluding sperm migration): 104 proven fertile men and 53 infertile men. Although subjective motility was able to predict from which group the sample came at optimum cut-off with 78% accuracy, computer analysed sperm velocity could predict with overall 91% accuracy at optimum cut-off.

Computer analysis of sperm velocity offers a rapid, objective and predictive assessment of sperm function.

Several authors have emphasised the value of sperm motility in determining the fertile quality of a semen specimen (Amelar *et al.*, 1980; Hargreave and Elton, 1983). The usual methods of evaluating this are subjective, although workers have attempted to standardise the technique by counting the motile and immotile sperms in 10 separate random fields away from the edge of the coverslip on a simple wet film preparation, preferably at 37°C. A subjective scale has been suggested for grading motility:

0 = No progression
1 = Weak forward progression
2 = Moderate forward progression
3 = Active forward progression

The subjective assessment of a wet film preparation of fresh well mixed semen has definite advantages: it is quick to perform and requires only a microscope.

Makler (1978) devised a photographic method with time-lapse exposure for objectively measuring sperm velocity. He used a simple stroboscopic light source composed of a 6-slotted disc rotated at 60 rpm between light source and condenser of the microscope. Using still photography and exposure of 1 s/frame, 6 pulses of light were produced of 1/200 s at intervals of 1/6 of a second. This ensured that motile spermatozoa would not be underexposed and immotile would not be over-exposed. This particular method appears to have an advantage over the method of Overstreet *et al.* (1979), where no such stroboscopic light source was used.

Holt *et al.* (1985) used a computer with graphics tablet and cursor linked to a video recorder and television monitor. Under standardised conditions a video recording of a semen sample can be analysed. This provides a very rapid objective measurement of mean sperm velocity and has been shown to correlate with *in vitro* fertilisation of hamster ova (Holt *et al.*, 1985).

A simple method of sperm migration was described by Hong *et al.* (1981); they used a transmembrane migration technique between 2 chambers separated by a nucleopore membrane containing 5 µm diameter holes. Fresh semen was

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placed in the upper chamber, which was then inserted into a bottle containing phosphate buffered saline. After incubation for 2 h at 37°C the sperm density was measured in the upper and lower chambers and the proportion of sperm that had moved down across the membrane could be calculated. They found that the transmembrane migration rate correlated well with subjective motility estimate of a wet film ($r = 0.96$).

## Materials and Methods

### *1. Subjective sperm motility*

Sperm motility was assessed on a droplet of well mixed semen placed in a 10 μm deep Makler well and examined with a × 20 objective lens using a Wild phase contrast microscope. The total number of sperms (motile and immotile) in 10 small squares of the Makler chamber were counted; the number of stationary sperms and those with weak forward progression within the same 10 squares was similarly counted (it being easier to count immotile than motile sperms) and by simple subtraction the number of motile sperms with moderate and active forward progression in the given 10 squares was obtained. The percentage motility was thus extrapolated. This was carried out in duplicate for each sample. All procedures were carried out at laboratory temperature (approximately 20°C).

### *2. Sperm velocity measurement by photographic time exposure*

Fresh well mixed semen was diluted to a sperm density of 10 M/ml in modified Biggers' solution (BWW). A drop was pipetted on to a Helber bacterial cell-counting glass slide with a 20 μm well and glass coverslip to give a uniform depth (Lamb and Co., Ltd). The preparation was allowed to equilibrate for 5 min. A stroboscopic effect was produced using a black disc with 6 equally distanced slits of 3 mm width driven by an electric motor at 1 rpm placed between the light source and the microscope condenser. Still photography was performed using a Nikon FI camera with 24 × 36 mm 400 ASA (27 DIN) black and white film (Ilford HP5). Initial photographic calibration was made at × 20 objective lens magnification of a phase contrast microscope (Nikon ELWD 0.3) with a standard graticule slide of 1 and 10 μm distances between lines. The uppermost layer containing most motile spermatozoa was placed in focus and 6 frames at × 20 magnification were filmed for a 1-s exposure time for each sample, moving the sample field per photographic frame. Thus 6 frames were exposed per sample. The photographic film was then processed and using a standard photographic enlarger, calibration was set so that 10 μm (from the standard graticule grid frame) were equivalent to 1 cm.

The progressively motile spermatozoa appeared as chains of 6 heads the length of which equalled the distance moved in 1 s. Tracks of motile spermatozoa were measured by joining the chains and measuring the chain length by ruler. Mean velocity (expressed as μm/s) for each sample was determined.

### *3. Sperm velocity measurement by computer analysis of a video recording of semen*

Fresh well mixed semen was diluted to a sperm density of 10 M/ml in BWW. A droplet was placed on to a Helber bacterial cell-counting slide with a 20 μm well and coverslip and the slide was placed on to a heated stage calibrated so that the well remained at 37°C. The specimen was allowed to equilibrate for 5 min to reach a constant temperature. A VHS video recording was made of the uppermost layer of the semen droplet at × 40 magnification of microscope objective for a duration of 5 min. Analysis of the video recording was made using a semi-automatic image analysis system (Analytical Measuring Systems Ltd, Saffron Waldon) which comprised an Apple II+ computer (Apple Computer Inc., Cupertino, USA) and an Apple graphics tablet linked to a video camera. The computer/camera interface allowed the projection of real-time images on to the television monitor screen along with the Apple text or graphics tablet displays.

The images of moving spermatozoa from the video recorder were thus displayed on the television monitor together with a mobile cursor controlled by the operator via the graphics tablet. Measurement of the sperm speed was achieved by tracking a chosen spermatozoon with the cursor. Each track was displayed as a series of points, 10 points/s being plotted. The computer programme was written to calculate a total length of track produced by the X and Y coordinates generated by the graphics tablet. The average speed of each spermatozoon was calculated from the distance travelled and the time taken to the nearest 0.1 s. (The distance had been previously calibrated from a recording of a standard graticule slide marked with lines at 1 and 10 μm).

To avoid sampling bias of the spermatozoa measured, a randomly positioned sampling box of 35 × 35 μm was displayed on the television monitor and the sperms tracked only if they issued from this box. The position of the box changed with each individual sperm measurement. Each spermatozoon was tracked over a distance of 100 to 200 µm. The computer automatically rejected any measurements completed in less than 1 s.

Thirty spermatozoa were samples per semen specimen, since it had already been established by Holt *et al.* (1985) that counting more produced little change in the values of mean velocity and standard deviation obtained.

### *4. Migration of spermatozoa across a nucleopore membrane*

100 µl of a fresh well mixed semen sample were pipetted into a tube made from the plunger of a 2 ml plastic syringe (Gillette Ltd) to which had been welded, by dipping the plunger into Xylene, a sheet of nucleopore membrane with 5 µm pores of 13 mm diameter. The tube containing the semen was placed into a 20 ml plastic pot containing 2 ml phosphate buffered saline at pH 7.3; the upper chamber's (tube) position was adjusted to a level so that the fluid levels of upper and lower chambers were equal. The apparatus was then incubated for 2 h at 37°C. The total number of spermatozoa was estimated in the lower chamber using the Makler 10 µm counting chamber; having previously determined the sperm density of the original sample by Makler chamber, the ratio of sperms that had migrated was calculated and expressed as a percentage: the transmembrane migration ratio.

### *Part 1: To assess and compare experimental error of the different methods*

Five fresh semen samples were split 5 ways to give 25 aliquots. These were randomly numbered and each examined by the 4 different methods. After completion the code was broken to reveal source.

### *Part 2: To assess the predictive value of different assessments of motility in determining fertile state*

Two groups of men were studied: a "fertile" and an "infertile" group. The fertile group (n = 104) consisted of partners of females in the post-natal ward of the London Hospital whose paternity had been proven with >95.5% certainty based on HLA-A-B and C antigen studies carried out on cord (child), maternal and paternal blood. All had conceived within 2 years of unprotected sexual intercourse (mean 4.8 months, SD 5.6).

The infertile group (n = 53) consisted of males of a primary infertile partnership in whom there was no known female cause for infertility based on ovulation and tubal patency studies. Those with azoospermia were excluded.

In both groups a single specimen of semen was produced by masturbation into a sterile plastic container whilst the subject was physically well following 3 days' sexual abstinence and submitted to the laboratory within 2 h of production.

The semen samples were analysed on arrival for subjective motility, sperm velocity by time-lapse photography and sperm velocity by computer analysis as outlined in Part 1. Following the results of Part 1, transnucleopore migration studies were not performed.

## Results of Part 1: To assess experimental error

*1. Subjective motility.* As shown in Table 1, a wide standard deviation (ranging from 7.9 to 17.3) was found in analysing the same sample, and coefficients of variation ranged from 24.09 to 38.5.

*2. Sperm velocity by time-lapse photography.* The results are shown in Table 2. Low standard deviation values were obtained from the same semen samples and the coefficient of variation ranged from 5 to 12.8%.

*3. Sperm velocity by computer analysis.* Table 3 shows that low levels of standard deviation, ranging from 0.77 to 1.2, were obtained from the same samples with coefficients of variation again low, ranging from 1.7 to 4.4%.

*4. Transnucleopore migration ratio.* Very wide standard deviations were found on breaking the code,

**Table 1** Subjective Motility Study: Experiment 1

| *Specimen* | *% Motility for the 5 randomised aliquots per specimen* | | | | | |
|---|---|---|---|---|---|---|
| I | 35)<br>42) 38.5 | 63)<br>59) 61 | 28)<br>35) 31.5 | 39)<br>43) 41 | 67)<br>71) 69 | Mean 48.2<br>SD 16.0<br>CV 33.2 |
| II | 15)<br>14) 14.5 | 28)<br>22) 25 | 17)<br>23) 20 | 41)<br>20) 30.5 | 37)<br>31) 34 | Mean 24.8<br>SD 7.9<br>CV 31.9 |
| III | 85)<br>88) 86.5 | 71)<br>63) 67 | 58)<br>43) 45.5 | 49)<br>61) 54.5 | 47)<br>58) 52.5 | Mean 61.2<br>SD 16.1<br>CV 26.3 |
| IV | 25)<br>30) 27.5 | 52)<br>46) 49 | 51)<br>58) 54.5 | 21)<br>19) 20 | 38)<br>31) 24.5 | Mean 37.1<br>SD 14.3<br>CV 38.5 |
| V | 100)<br>96) 98 | 72)<br>65) 68.5 | 58)<br>63) 60.5 | 78)<br>61) 69.1 | 56)<br>58) 52 | Mean 69.6<br>SD 17.3<br>CV 24.9 |

**Table 2** Accuracy of Time-lapsed Photography Velocity Method

| *Specimen* | | | | | | *Mean* | *SD* | *CV (%)* |
|---|---|---|---|---|---|---|---|---|
| A | 31 | 29 | 29 | 32 | 31 | 30 | 2.0 | 6.7 |
| B | 17 | 21 | 22 | 23 | 18 | 20.2 | 2.6 | 12.8 |
| C | 48 | 47 | 44 | 49 | 44 | 46.4 | 2.3 | 5.0 |
| D | 52 | 57 | 58 | 54 | 59 | 56 | 2.9 | 5.2 |
| E | 39 | 41 | 42 | 37 | 40 | 39.8 | 1.9 | 4.8 |

**Table 3** Accuracy of Computer Analysis of Sperm Velocity

| *Specimen* | | | | | | *Mean* | *SD* | *CV (%)* |
|---|---|---|---|---|---|---|---|---|
| A | 44.2 | 45.6 | 45.2 | 46.3 | 45.6 | 45.4 | 0.77 | 1.7 |
| B | 21.6 | 21.6 | 21.5 | 23.8 | 22.3 | 22.2 | 0.97 | 4.4 |
| C | 12.5 | 13.3 | 12.6 | 12.0 | 12.9 | 12.7 | 0.48 | 2.4 |
| D | 40.4 | 41.4 | 42.8 | 42.9 | 41.2 | 41.8 | 1.0 | 2.6 |
| E | 31.4 | 32.0 | 30.9 | 29.1 | 31.8 | 31.0 | 1.2 | 3.9 |

ranging from 3.2 to 41.3, with high coefficients of variation ranging from 15.7 to 69.8.

### Results of Part 2: To assess the predictive value of the different methods of sperm motility assessment

The distribution of values obtained in the 2 populations for subjective motility is shown in Figure 1, for sperm velocity measurement by time-lapse photography in Figure 2 and sperm velocity by computer analysis in Figure 3.

The Mann-Whitney U test was applied to the data. For all 3 methods there were significant differences between the 2 groups (fertile and infertile) for subjective motility ($P<0.001$), time-lapse photography ($P<0.001$) and computer analysis ($P<0.001$).

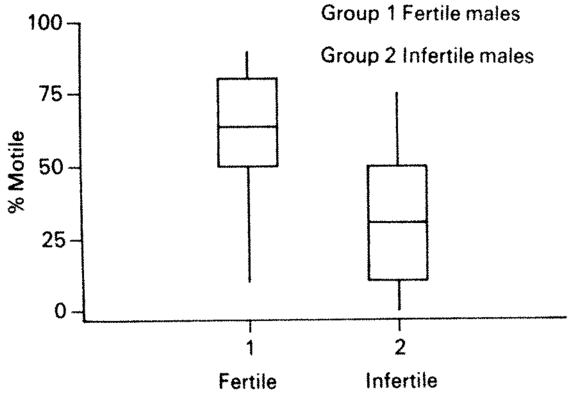

**Fig. 1** Distribution of subjective assessment of sperm motility.

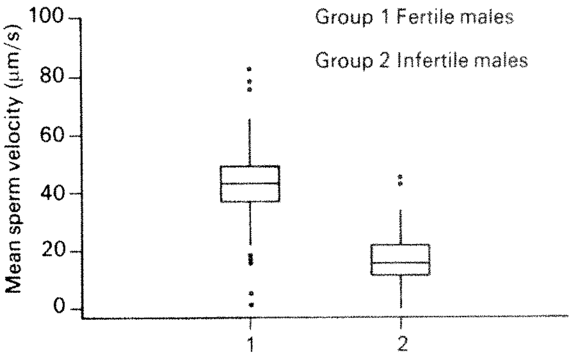

**Fig. 2** Distribution of sperm velocity by computer analysis.

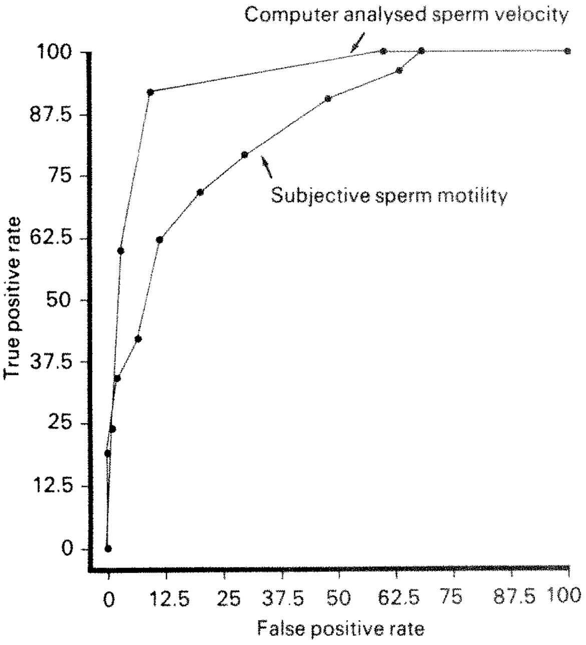

**Fig. 3** Receiver operating characteristic curve (ROC) for motility.

Spearman's correlation coefficient was calculated from the results combining the 2 groups (fertile and infertile). There was positive correlation between subjective motility and time-lapse photography ($r=0.56$) and computer analysis ($r=0.54$). There was a strong positive correlation between the 2 methods of sperm velocity measurements ($r=0.83$).

The predictive value of the tests was analysed using a stepwise discriminant analysis (computer program BMD P7M) (Dixon *et al.*, 1981). Sperm velocity by time-lapse photography was not considered because 34% of the total data could not be analysed, the films being uninterpretable. The results are shown in Table 2. Mean sperm velocity by computer was able to distinguish between fertile and infertile populations and vice versa with 91% accuracy at optimum cut-off point, whereas subjective motility could predict with only 78% accuracy at optimum cut-off point. The difference in sensitivities of the 2 methods is best visualised in Figure 3, which shows the curve produced by plotting true positive rate against false positive rate for the 2 methods at different cut-off points. In order for the test to be ideal it should approach a ratio between a true positive and false positive rate of 1.0, that is the curve should be close to the top left hand corner. As can be seen, the computer analysed method approximates well, whereas subjective sperm motility performs less well.

## Discussion

Sperm motility as part of semen analysis has been emphasised as having prognostic value in determining fertility (Hargreave and Elton, 1983). Jequier and Ukombe (1983) pointed out that such analyses may be inaccurate.

Our results confirm the findings of Jequier and Ukombe (1983) that subjective assessment of sperm motility is relatively inaccurate even when using a standardised system incorporating the Makler chamber and thus avoiding the need for dilution of the semen sample.

Transnucleopore migration was found to be extremely inaccurate and cannot be recommended.

Although the time-lapse photography method was repeatable and accurate and involved less initial capital expense than the computer analysis system, it was found to be more cumbersome, was unable to give instant results and many of the photographic frames were uninterpretable. Its use is thus very limited.

The computer analysis system is easy to perform, rapid, and gives an instant measure of sperm velocity; each computer analysis of the video recording took less than 15 min per specimen to perform.

In the second part of the study there were significant differences in sperm motility and mean sperm velocity analysed by either method for the 2 groups. When a multivariable discriminant analysis was undertaken, the computer analysis system was able to detect fertile status with 91% accuracy.

Over 90% of the fertile men had a mean sperm velocity >30 μm/s and more than 95% had a mean sperm velocity value >25 μm/s. Conversely, in the infertile group only 6% had a mean sperm velocity >30 μm/s and 2% >40 μm/s.

The need for accurate and predictive methods in semen analysis has been heightened by the recent developments of *in vitro* fertilisation and gamete intra-Fallopian tube transfer (GIFT) techniques. As well as the need to select patients who may benefit from such sophisticated and expensive techniques and to eliminate those who will not, objective tests of sperm function are also needed to substantiate or deny the many claims for drug treatments in male infertility and the value or otherwise of varicocelectomy. The measurement of mean sperm velocity by computer analysis is a good diagnostic test of sperm function.

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# The Scrotoscope. A New Instrument for Examining the Scrotal Contents

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Summary—A new instrument (the scrotoscope) is described. It was used in the diagnosis of questionable masses in the testis, epididymis and spermatic cord in 49 patients. Scrotal examination and testicular biopsy were performed in 31 infertile patients by means of the scrotoscope, together with pampiniform plexus venography in 1 patient and vasography in 2. Scrotoscopy allows the surgeon to view, study and treat intrascrotal lesions.

The scrotoscope was designed for the diagnosis and treatment of intrascrotal lesions (Shafik, 1986). The author's further experience with this instrument is now presented.

The scrotoscope consists of a sheath, telescope, obturator and accessories. The sheath is 5.5 mm in diameter with 2 stopcocks to control inflow and outflow. The telescope has a 30° forward oblique angle, a diameter of 4 mm and a fibreoptic light transmission incorporated. The accessories include biopsy cutting forceps and scissors. The scrotoscope is manufactured by the Arab Organization for Industrialization, Cairo, Egypt.

## Patients and Methods

Scrotoscopy was performed in 83 patients aged between 28 and 65 years (average 38). The scrotoscope was used to examine the intrascrotal contents and to take biopsies from masses in the spermatic cord in 32 patients, in the testis in 6 and the epididymis in 11. The cord masses proved to be bilharzial in 26 patients and filarial in 6. Of the 6 testicular masses, 4 were malignant and 2 were filarial. The epididymal masses were bilharzial in 6 and tuberculous in 5. Scrotal examination was performed in 31 infertile patients and testicular biopsies taken. The scrotoscope was also used to carry out pampiniform plexus venography in 1 patient and vasography in 2 azoospermic patients.

Before carrying out scrotoscopy, the scrotal skin and intrascrotal structures should be examined to define the exact site of the pathological lesion. The procedure should be done under sterile conditions with the patient in a supine position. Either local or general anaesthesia is administered. The former is preferred because it has a lower morbidity rate and can be done on an out-patient basis. The skin and subcutaneous tissue at the fundus of the scrotum are infiltrated with 5 ml 0.5% lignocaine (Xylocaine). An additional 5 ml are injected directly into the spermatic cord; 1 litre of normal saline in a closed system is connected to the inflow valve of the sheath.

A small incision (5 mm) is made in the skin and superficial fascia. The sheath with the blunt obturator in place is passed through the incision. The scrotum is distended with 40 to 60 ml saline and the inside of the scrotal wall checked while the instrument is advanced. The testis, epididymis and spermatic cord are examined from the anterior, posterior and both lateral aspects.

Operating forceps can be used blindly through the sheath (upon removal of the telescope) or under direct vision by inserting an auxiliary sheath through a second portal of entry. The latter procedure allows the operating tools to be visualised and a swelling can be either removed or biopsied under direct vision. After scrotoscopy, the patient

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is given an antibiotic for 24 h and advised to wear a scrotal support for 2 to 3 days.

## Results

Oedema of the subcutaneous scrotal tissues occurred in some patients following scrotoscopy but this disappeared in 3 to 4 days. It seemed to result from distending the scrotum with saline during endoscopy. Scrotal haematoma occurred in 1 patient in whom a testicular mass was biopsied; it absorbed spontaneously. No other complications were encountered.

### *Contraindications*

There is no contraindication except in scrotal skin infections. In such cases, scrotoscopy should be postponed until the infection has been eradicated. Septic orchitis, epididymitis and funiculitis are not contraindications; they can be inspected with the scrotoscope and subsequently cultured.

## Discussion

Scrotoscopy was used to visualise and take biopsies from questionable masses in the testis, epididymis and spermatic cord in 49 patients. No complications were encountered except for a scrotal haematoma in 1 patient.

The scrotoscope enabled intrascrotal lesions to be diagnosed easily and their pathological nature verified. Morphological changes in the testis, epididymis and masses, *e.g.* haemorrhagic and degenerative areas, could be visualised and biopsied, although they were not detected clinically. Cystic swellings were readily differentiated from solid masses.

Scrotoscopy was performed in 31 infertile patients. In cases of varicocele, tortuous veins were seen over the testis but were easily avoided when biopsying the testis with the scrotoscope. Multiple small cysts were encountered in the head of the epididymis in some infertile patients; they were punctured and their contents examined and cultured.

Scrotoscopy played an important role in the radiodiagnosis of scrotal lesions. It was helpful during injection of dye into the vas deferens for vasography (2 patients) and into the pampiniform plexus for venography (1 patient). There were no complications. This is in contrast to blind vasography and venography, which are not only time-consuming but may also lead to considerable damage to the vas or pampiniform veins.

Repeat scrotoscopy allows intrascrotal lesions to be monitored, surgery to be properly timed and non-surgical treatment to be carried out with greater assurance. It enables sequential testicular biopsies to be taken without undue injury. Epididymal biopsies were also performed with the least possible injury to the epididymis.

The evolution of various diseases of the testis, epididymis or spermatic cord can be studied by means of scrotoscopy. This is of particular interest in bilharzial and filarial lesions, which often involve the intrascrotal structures. These lesions pass through clinicopathological stages that can be readily defined by scrotoscopic examination and biopsy, allowing treatment to be planned accordingly.

Scrotoscopy also makes it possible to detect complications early and study the healing process of the vas deferens when reanastomosed after being ligated for birth control. The patency of the vas in obstructive infertility and of the stoma of epididymovasal anastomosis could be assessed in a similar way. These aspects are currently under investigation.

### *Intrascrotal surgery*

Excision of testicular, epididymal or cord masses and cysts, and drainage of testicular abscesses or secondary hydroceles can be managed through the scrotoscope. Cysts were punctured and their fluid contents examined and cultured. The varicose veins of 6 varicocele patients were injected under scrotoscopic control without undue damage to the spermatic cord or haematoma formation, as may occur during blind injection. Cord lesions can be treated regardless of whether they are in the scrotum or the inguinal area. Vasal ligation can also be performed through the scrotoscope.

The use of local anaesthesia makes scrotoscopy for diagnosis or therapy a simple out-patient procedure. However, scrotoscopy is not meant to replace good history-taking and a thorough physical examination. These steps remain prerequisites to any diagnositc study.

## Acknowledgement

The valuable assistance of Mrs Margot Yehia in revising the manuscript is highly appreciated.

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*British Journal of Urology* (1990), **65**, 211–217

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# Case Reports

## Infected Hydrocele Following Acute Appendicitis

A. A. CHRYSOSTOMOU, P. J. PHEILS and B. A. PRICE, *Department of Surgery, Thanet District General Hospital, Margate*

### Case Report

A 9½-year-old boy presented with abdominal pain, anorexia and general malaise of 1 week's duration. He complained of nausea and had vomited twice. Examination revealed an unwell, mildly dehydrated child with a temperature of 37.7°C, pulse 100/min and a marked foetor. The abdomen was maximally tender with guarding in the right iliac fossa. Rectal examination revealed pelvic tenderness. The genitalia were normal and there were no obvious herniae. Urine microscopy was clear.

A gangrenous perforated appendix was removed on the day of admission and the surrounding abscess drained. Cefuroxime 250 mg 8-hourly and metronidazole 200 mg 8-hourly were commenced intravenously. Peritoneal swabs grew significant numbers of *Escherichia coli* and *Bacteroides* spp. sensitive to these drugs respectively.

The patient progressed well post-operatively but maintained a persistent pyrexia until the sixth post-operative day, when he developed a reddened, tender swelling of the left side of the scrotum. The cord was not tender and urine microscopy examination was again clear. At exploration a pus-filled hydrocele surrounding an injected but otherwise normal testis was found. A fine probe could be passed easily up into the peritoneal cavity through a patent processus vaginalis.

The fibrinous exudate surrounding the testis was removed, a corrugated rubber drain inserted into the tunica sac and the wound closed. He progressed well after this and his temperature returned to normal. The antibiotics were continued for a further week, the drain was removed at 48 h and after a total of 12 days in hospital he was discharged. Culture of the scrotal pus failed to produce growth of organisms. At follow-up 2 weeks later he was found to be fully recovered with soundly healed wounds.

### Comment

The onset of acute severe scrotal pain with the presence of inflammatory signs in children and adolescents is an emergency requiring surgical exploration if only to exclude testicular torsion (Kaplan and King, 1970). An infected hydrocele following acute appendicitis is rare (Nagel, 1984); 4 of the 5 cases in the literature varied in age from 10 weeks to 2½ years and presented primarily with scrotal signs. The intra-abdominal pathology was discovered only after exploration of the scrotum. The remaining case resembled ours in that the scrotal manifestations occurred 3 days following appendicectomy for acute appendicitis in a 7-year-old boy (Waldbaum and Green, 1973).

This case emphasises the importance of the painful red scrotum in children. We have not planned for herniotomy in this child unless he develops an obvious hernia. We will continue to watch expectantly but it may be that infection of the sac lining will have led to its obliteration.

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## Squamous Metaplasia Complicating a Müllerian Duct Remnant

G. G. YOUNGSON, *Department of Surgery, Royal Aberdeen Children's Hospital, Aberdeen*

### Case Report

A 4-year-old boy was referred to hospital with a single urinary tract infection because blood, a large amount of pus and *Escherichia coli* were present in the urine. The child was clinically well but a large mass, resembling an obstructed urinary bladder, was palpated in the lower abdomen. His external genitalia were normal.

Ultrasound defined a large (15 × 10 cm) thick-walled cystic mass between rectum and bladder compressing the latter and extending above the umbilicus; the urinary tract and pelvic contents were otherwise normal. At urethroscopy a 3 F retrograde catheter passed easily through the prostatic utricle into a grossly distended Müllerian duct remnant and released large volumes of

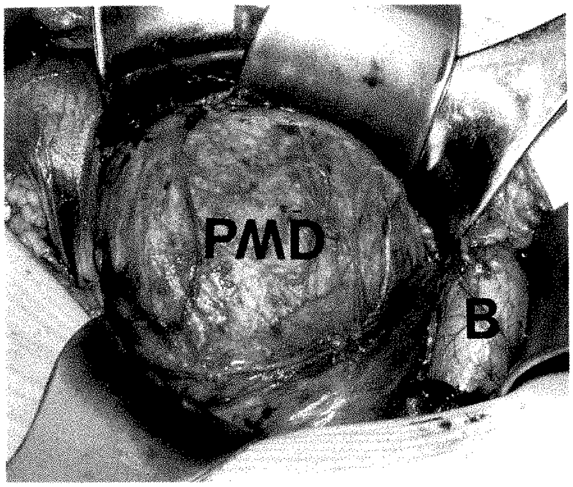

**Fig.** Operative view of bladder (B) and persistent Müllerian duct remnant.

foul smelling pus, culture of which produced a pure growth of *Bacteroides fragilis*.

Through a transabdominal extraperitoneal approach (Fig.) the remnant was excised down to the level of the prostatic urethra. The patient's recovery was uncomplicated and the operation caused no voiding dysfunction.

Histological examination confirmed the lesion to be a persistent Müllerian remnant whose epithelium exhibited squamous metaplasia at varying sites.

## Comment

Opinion on treatment for Müllerian duct remnant in the male tends towards a conservative approach (Felderman *et al.*, 1987). However, the recommendation that the vaginal component, when it exists in isolation, should be excised only if symptomatic (Morgan *et al.*, 1979) should be reconsidered in view of the histological change which occurred in this case. Squamous carcinoma is already recognised as a complication of this anomaly (Szemes and Rubin, 1968).

## Acknowledgements

The author thanks Dr Rankin, Department of Pathology, Medical Illustration Department, Aberdeen University Medical School, and Miss Moir, research secretary, Aberdeen Royal Infirmary, for their help in preparation of the article.

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# A Rare Cause of Post-micturition Dribbling: Incomplete Urethral Duplication

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## Case Report

A 38-year-old General Practitioner presented with a 4-year history of gross post-micturition dribbling. He obtained some relief by double voiding whilst sitting. Investigation elsewhere by intravenous urography and cystoscopy was inconclusive. A micturating cystourethrogram revealed a 4-cm incomplete urethral duplication involving the bulbar urethra with a thin septum between the primary urethra and the duplicated urethra (Fig.).

At urethroscopy, the accessory urethra was seen through the septum and appeared to communicate with the primary urethra proximally. The septum was divided using a right-angled diathermy electrode. The patient was discharged home the following day with an indwell-

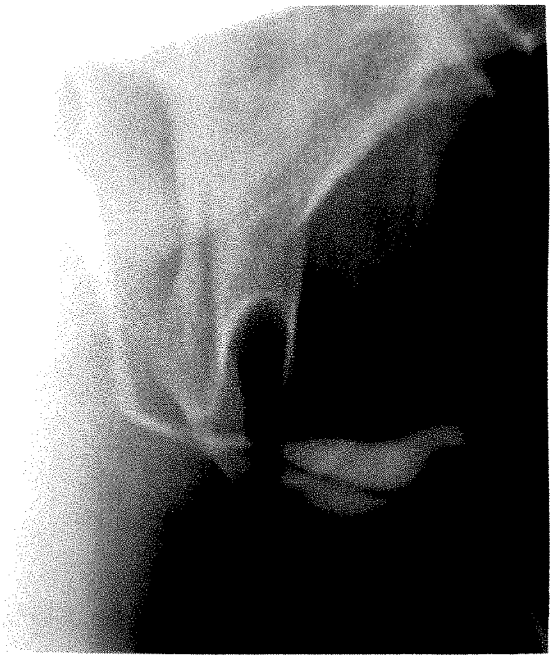

**Fig.**

ing urethral catheter which was removed after 7 days. Continence was immediately and completely restored and the patient remains continent.

### Comment

Duplication may be either complete or incomplete, communicating or non-communicating. If incomplete, the accessory urethra arises from the primary urethra and may or may not have an external opening. A further anatomical type, in which one of the duplicated urethras arises from the bladder or proximal urethra and opens into the perineum, has been described (Cullen, 1973; Das and Brosman, 1977). Incomplete communicating urethral duplication causes post-micturition dribbling because of the overflow of "voided" urine from the accessory to the primary urethra, as in the present case. Micturating cystourethrography is the most effective way of diagnosing this unusual cause of post-micturition dribbling (Hoekstra and Jones, 1985).

### Acknowledgements

We thank Mr B. J. Abel for allowing us to report this case and Miss M. Gibson for typing the manuscript.

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## Refrigeration Engineer's Testis

B. W. SCOTT and M. J. GOUGH, *Department of Surgery, Royal Infirmary, Bradford*

### Case Report

A 25-year-old man who was employed to maintain large "walk-in" refrigeration units presented with a 1-year history of testicular pain and retraction when working in a cold environment and after sexual intercourse.

Examination of the scrotum, testes, and hernial orifices was normal but the cremasteric reflex was exaggerated and both testes retracted into the groin.

Since the patient felt unable to continue in employment, surgical treatment was undertaken. Under general anaesthesia the spermatic cord was exposed and a circumferential cremasteric myotomy performed. Eighteen months later the patient remains asymptomatic.

### Discussion

An exaggerated cremasteric reflex is a common cause of apparent cryptorchidism in childhood. However, the condition of symptomatic retractile testes in an adult requiring surgical treatment does not seem to have been reported previously.

Occupational factors were undoubtedly relevant to the development of symptoms in this patient.

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## Squamous Cell Carcinoma in a Patient on Clean Intermittent Self-catheterisation

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We report a case of squamous cell carcinoma of the bladder (SCC) occurring in a patient performing clean intermittent self-catheterisation (CISC).

### Case Report

Mrs. H.B., aged 69 years, who had practised CISC for 4 years for an underactive bladder, presented with a 4-month history of intermittent haematuria, pain on catheterisation and suprapubic pain. Several courses of antibiotics failed to relieve her symptoms or eradicate her persistent bacteriuria. Cystoscopy revealed a large ulcerated tumour in the dome of the bladder where the catheter impinged. Biopsy showed SCC. She underwent cystectomy and urinary diversion and made an uneventful recovery. Histopathological examination showed a 6 × 5 cm SCC in the dome with squamous metaplasia and dysplasia amounting in places to carcinoma *in situ* up to 5 cm away from the main tumour. The epithelium further away was transitional in type. Four weeks after discharge she collapsed and died of a perforated duodenal ulcer. Post mortem showed no evidence of metastatic tumour.

## Comment

CISC is a well established treatment in certain patients with underactive bladders. Studies have shown that SCC can develop in patients who have had indwelling catheters for several years (Locke *et al*., 1985). In several large studies on patients on CISC no case of SCC has been described and we believe this to be the first on record. Although asymptomatic bacteriuria is frequent, symptomatic infection is rare if the bladder is being emptied completely (Diokno *et al*., 1983). In many cases of SCC there is delay in diagnosis, usually because the condition is associated with recurrent urinary infections (Rous, 1978). We recommend that patients on CISC undergo cystoscopy regularly especially if symptoms arise. The pathogenesis of SCC in this patient and in others with long-term indwelling catheters remains unclear. However, the fact that in this patient the bladder epithelium distant from the tumour remained transitional in type suggests that direct impingement by the catheter was highly significant.

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## Fibroepithelial Polyps of the Pelviureteric Junction in Childhood

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### Case Reports

*Case 1.* A 5-year-old boy was admitted for evaluation because of multiple episodes of intermittent left flank pain associated with microscopic haematuria. He also had an undocumented history of passing stone-like debris in his urine. Physical examination revealed mild left flank tenderness but was otherwise normal. Routine serum chemistry, CBC were normal. Urine analysis showed trace of protein with microscopic haematuria but no growth. Abdominal ultrasound showed moderate left hydronephrosis and a voiding cystourethrogram showed no vesicoureteric reflux. IVU revealed a left hydronephrosis with mild diminution of the overlying cortical tissue. No contrast was seen in the left ureter up to 1 h and a diagnosis of pelviureteric junction (PUJ) obstruction was made. At surgery, cystoscopy was normal but on retrograde injection the contrast did not pass the PUJ. The renal pelvis was explored and a small ureteric polyp (2 × 1 cm) was found arising from the PUJ and extending down to the ureter (Fig. 1). The polyp was resected and a dismembered pyeloplasty performed. The patient recovered uneventfully and has had no recurrence of symptoms during a 5-year follow-up. Microscopic examination of the polyp showed a normal lining of transitional epithelium with a fibrous tissue core consistent with the diagnosis of benign fibroepithelial polyp.

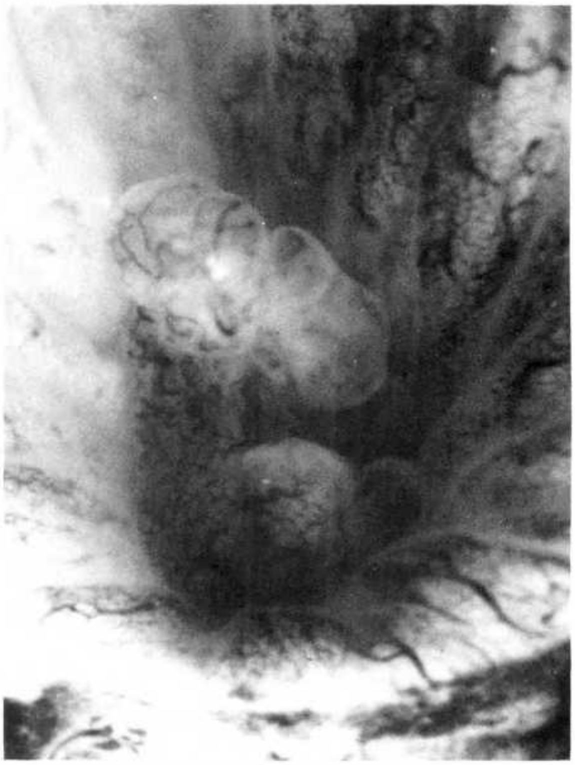

**Fig. 1** Case 1. Intra-operative view shows the pedunculated fibroepithelial polyp arising from the pelviureteric junction and extending into the ureter.

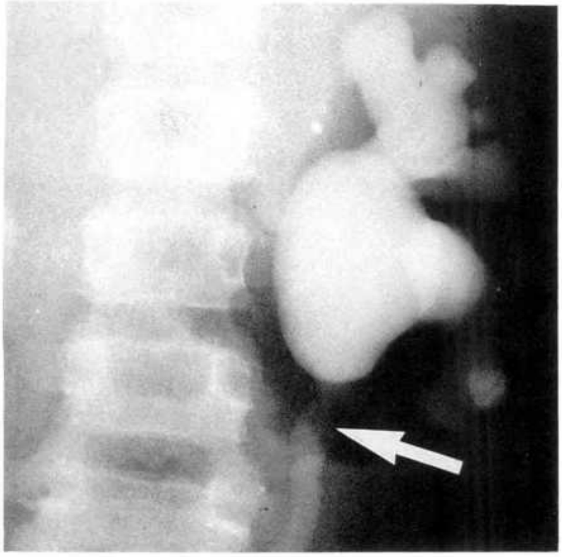

**Fig. 2** IVU shows spontaneous drainage on the left side with mild upper tract dilatation and a filling defect in the left pelviureteric junction (arrow).

*Case 2.* A 9-year-old boy presented with abdominal pain accompanied by nausea and vomiting. He had had multiple previous episodes of similar symptoms which resolved spontaneously with bed rest. Physical examination was normal except for moderate flank tenderness. Urine analysis, serum chemistry, CBC were all normal. Abdominal ultrasound showed a marked left hydronephrosis and an IVU revealed delayed drainage with a questionable mass lesion at the left PUJ (Fig. 2). A voiding cystourethrogram was normal. At cystoscopy the bladder was normal but the left retrograde pyelogram showed obstruction at the PUJ area with no contrast passing into the renal pelvis. On exploration the renal pelvis was mildly distended and a pedunculated polypoid lesion was found arising from the PUJ and extending into the proximal ureter. It was resected and a dismembered pyeloplasty performed. Histological examination revealed a fibroepithelial polyp with no evidence of malignancy (Figs 3, 4). The patient recovered uneventfully and had no recurrence of symptoms 6 months later.

## Comment

Fibroepithelial polyp is a rare benign tumour arising from the wall of the urinary tract at various locations from renal pelvis to urethra. Most patients are asymptomatic until the tumours become large and mobile enough to cause obstruction. Fibroepithelial polyps have been reported in all age groups but only 16 cases of benign fibroepithelial polyps of the ureter have been reported in children less than 18 years old (Mydlo *et al.*, 1988). The most common location is the upper ureter (62%), especially the pelviureteric junction, and the middle and lower thirds of the ureters account for the remaining 38% (Stuppler and Kandzari, 1975). Typical symptoms include flank pain in 41% of patients and haematuria (gross and microscopic) in 39%. Physical examination usually fails to reveal specific findings other than flank tenderness. No specific laboratory test, urine analysis or cytology studies add to the diagnosis.

Routine abdominal imaging using abdominal ultrasound and IVU usually reveals obstruction which can be difficult to differentiate from classical PUJ obstruction. In our 2 patients, although ultrasound studies demonstrated hydronephrosis, the polyps were not seen even with careful retrospective review of the ultrasound images. In 1 patient the IVU showed questionable presence of a filling defect at the PUJ with mild dilatation of the

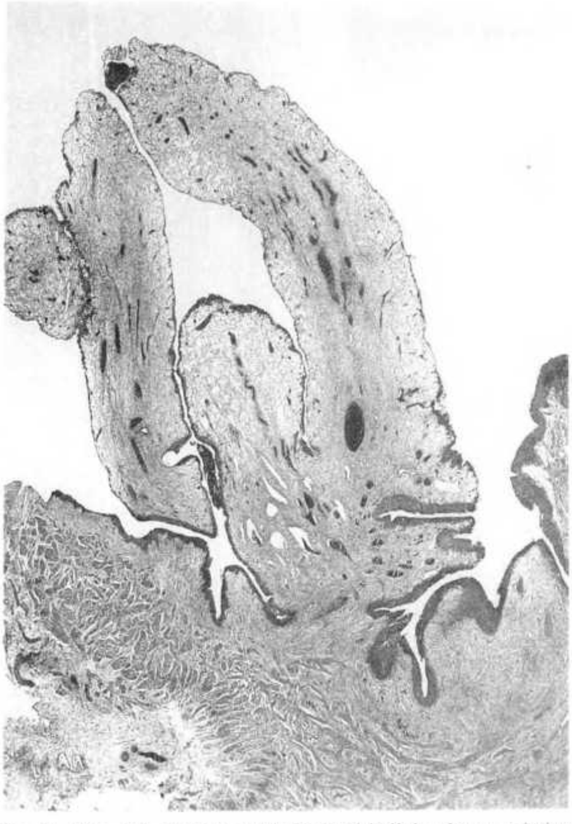

**Fig. 3** Segment of ureter with fibroepithelial polyp consisting of fibrovascular stroma with normal urothelial lining. (H and E × 20).

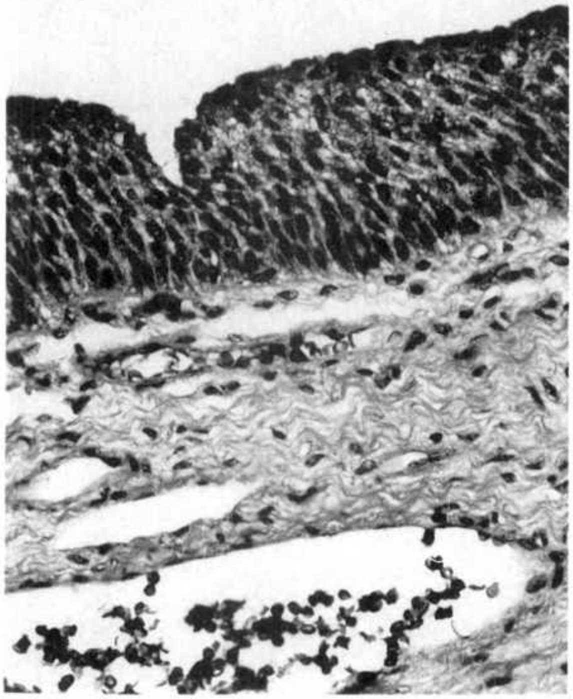

**Fig. 4** Higher magnification of the polyp showing benign urothelial lining and fibrovascular stroma. (H and E × 250).

upper ureter, which is an atypical finding in patients with simple PUJ obstruction. When the ureter is not clearly seen, retrograde pyelography is indicated at the time of cystoscopy.

Resection of the polyps and dismembered pyeloplasty was successfully performed in both of our patients. Although PUJ percutaneous endopyelotomy has been described for patients with PUJ obstruction (Badlani *et al.*, 1986), we feel that this procedure would not have completely removed the polyps in our patients.

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# Ruptured Bladder Following Circumcision Using the Plastibell Device

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## Case Report

A 5-year-old healthy boy underwent ritual circumcision under local anaesthesia by a family doctor using a Plastibell device.

Post-operatively the patient suffered severe abdominal pain followed by anorexia, nausea and vomiting. When he had not passed urine for 48 h he was referred to hospital. On admission he was drowsy, dehydrated and exhibited Kussmaul breathing. Abdominal examination suggested free fluid in the peritoneal cavity with bilateral loin and suprapubic tenderness. The Plastibell device was still *in situ* and the glans was encrusted with blood. Serum chemistry indicated a profound metabolic acidosis, with hyperkalaemia of 7.7 mmol/l, hyponatraemia (125 mmol/l) and elevated urea and creatinine levels of 49 mmol/l and 659 µmol/l respectively. The clinical diagnosis of urinary ascites was supported by signs of free fluid on abdominal X-ray and the aspirated ascitic fluid was chemically similar to urine.

The Plastibell device was removed and the patient catheterised. Retrograde cystography demonstrated an intraperitoneal bladder rupture. At exploration a small tear in the dome of an otherwise normal bladder was repaired. No evidence of pre-existing bladder pathology was found. An uneventful recovery followed.

## Comment

We are not aware of ruptured bladder following circumcision having been reported before. Neonatal bladder rupture secondary to distal obstruction has been reported (Johanson, 1982). So-called spontaneous rupture of the bladder almost invariably occurs in the pathological organ (Thompson *et al.*, 1965). This case brings into sharp focus the use of the Plastibell device, which in our experience has a relatively higher complication rate when used as a substitute for formal circumcision by family practitioners (Millar and Roberts, 1987), although others have found it satisfactory (Fraser *et al.*, 1981). Careful technique and post-operative supervision in circumcision remain vital despite the use of such devices.

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# Primary Squamous Carcinoma of the Male Urethra Presenting as a Periurethral Abscess

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## Case Report

A 68-year-old retired maintenance worker presented with a 3-week history of increasing pain and swelling in his perineum. He had been treated with 3 courses of antibiotics by his family doctor with no improvement. He had no urinary symptoms and no past history of venereal disease. He had had a routine TURP 4 years previously without complications.

Examination revealed an oedematous, red scrotum with a tender mass at the penile base, and inguinal lymphadenopathy. Pus was aspirated from the perineal swelling. At urethroscopy the urethra was found to be impassable and grossly disorganised. Formal incision and drainage of the abscess and suprapubic catheterisation were performed. The presumptive diagnosis was of an abscess secondary to a stricture and the patient was discharged to allow the inflammation to settle. He was readmitted 2 weeks later as an emergency with further urethral discharge and increased perineal swelling. Urethroscopy was repeated and biopsies taken from the urethra and the perineum revealed a well differentiated squamous cell carcinoma.

Further investigations, including chest X-ray, IVU and cystoscopy (via the suprapubic cystostomy), were all normal.

Penectomy and bilateral orchiectomy were performed 4 weeks after presentation. There was extension of tumour through the perineal membrane. This was later confirmed by CT scanning, which also showed pelvic lymph node enlargement. The patient was referred for radiotherapy.

## Comment

Squamous cell carcinoma of the male urethra is a rare disease and accounts for less than 1% of all urological malignancies. Since the initial description in 1834, approximately 600 cases have been reported (Kaplan *et al.*, 1967; Hopkins *et al.*, 1984).

This case illustrates the importance of biopsy in periurethral abscesses which behave atypically.

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# Point of Technique

## Simple Method of Hydrostatic Dilatation of the Ureter for Ureteroscopy

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Dilatation of the ureteric orifice and intramural ureter is usually necessary for ureteroscopy. Methods used include indwelling ureteric stents, graded dilators and balloon catheters (Bagley, 1988). Alternatively, hydrostatic dilatation can be used, although purpose-built infusion pumps are expensive. We describe a simple and cheap method of ureteric hydrostatic dilatation.

### Technique

A gravity feed irrigation system is attached to 1 of the 2 inlet ports of the ureteroscope. The other port is connected to a litre bag of saline via an intravenous giving set. The bag is pressurised to 150–300 mmHg using an inflatable pressure infusor (more usually used for the rapid infusion of intravenous fluids) (Fig.).

The ureteroscope is lodged in the ureteric orifice and the pressurised irrigation turned on. The effect of the high pressure stream is to open the ureter ahead of the instrument and also to flatten the ureteric mucosa and prevent mucosal folds obstructing advancement. Once the ureteroscope has traversed the intramural ureter the pressurised irrigation is turned off and the gravity fed system used. Prophylactic antibiotics are given with the premedication.

### Results

The technique was used in 12 patients (7 ureteric stones, 3 diagnostic explorations and 2 ureteric stent retrievals). Successful instrumentation was achieved in 11 cases, although in 1 of these a stone was flushed back into the kidney and not retrieved; 5 patients have had intravenous urograms 3 months post-operatively, all of which showed normal excretion and ureteric anatomy. This method of hydrostatic ureteric dilatation appears to be a simple, cheap and effective means of dilating the intramural ureter during ureteroscopy.

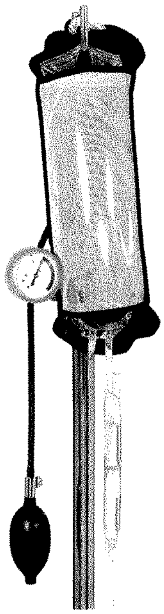

**Fig.** A pressure infusor of the type used for hydrostatic ureteric dilatation.

### Acknowledgements

We are grateful to Messrs M. Handley Ashken, C. G. C. Gaches and N. A. Green for their assistance with this study.

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# Notices

## British Association of Urological Surgeons

**President:** R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

*Annual Meeting: Scarborough. 10–13 July 1990*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

## European Society of Paediatric Urology

Founded in June 1989, this Society aims to promote paediatric urology by means of clinical co-operation between paediatric urology departments (exchanges, prospective/randomised studies, data banks), research programmes, annual meetings (see Diary page), creation of an autonomous educational training programme and grants for training.

The President is Professor R. Scholtmeijer (Rotterdam), General Secretary Dr P. Mouriquand (Lyon), Treasurer Dr J. de Vries (Nijmegen), and the two Members of the Board are Dr R. Nijman (Rotterdam) and Mr P. Duffy (London).

For further information please contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.

## Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

## Second Copenhagen Symposium on Uroradiology

*Herlev, Denmark. 27–30 August 1990*

The following topics will be included: Upper urinary tract imaging and intervention; Contrast medium nephrotoxicity; Hydronephrosis/obstruction; The urinary bladder; Genital radiology; The adrenal glands; Free communications.

## International Continence Society: 20th Annual Meeting

*Aarhus, Denmark. 12–15 September 1990*

Further information from: Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

## Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

*British Journal of Urology* (1990), 65, 220–221

# Diary

1990

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|---|---|
| March 15–16 | **Course in Urological Computing. Walton Conference Centre, Southern General Hospital, Glasgow. The second day of the course will be combined with the Fourth Annual Meeting of the Urological Computing Society. Contact Mr E. S. Glen, Urology Department, Southern General Hospital, Govan Road, Glasgow G51 4TF. Tel. 041 445 2466. Fax 041 445 3670.** |
| March 15–16 | Computers and Information Technology in Urology. Glasgow. Contact Mr E. S. Glen, Department of Urology, Southern General Hospital, Glasgow G51 4TF. Tel: 041 445 2466. |
| March 16 | Early Prostatic Cancer—Which Treatment? Newport, Gwent. Contact Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ. |
| March 19 | **BAUS One Day Symposium on Endoscopes, Video Equipment, Teaching Aids and Accessories. Whittington Hospital, London. Contact BAUS Office, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.** |
| March 21–23 | International Conference on Early Prostatic Cancer. Stockholm, Sweden. Contact the WHO Collaboration Centre for Urological Tumours, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden. |
| March 22–23 | Journées Urologiques de l'Hôpital Necker, Paris, France. The topics will be Renal Artery Surgery and Pathology of the Testis and Spermatic Cord in Childhood. Contact Madame M. C. Brandt, Secrétariat du Professeur Cukier, Clinique Urologique, Hôpital Necker, 149 rue de Sèvres, 75743 Paris, France. |
| March 28–30 | **Association of Surgeons of Great Britain and Ireland. Annual Meeting. Cardiff. Closing dates for abstracts 7th October 1989. Contact Ms Caroline Ross at the Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 3474** |
| April 22–26 | 18th Biennial Congress of the Urological Association of South Africa. Durban, South Africa. Contact Uro 1990, P.O. Box 17008, Durban 4013, South Africa. |
| April 27–28 | Interactive Obstructive Uropathy. Manchester. Contact Mrs G. Trimble, Department of Urology, Withington Hospital, West Didsbury, Manchester M20 8LR |
| May 5–6 | Athenian Days of Urology 1990. Athens, Greece. Contact Professor C. Dimopoulos, Department of Urology, Laiko Hospital, 115 27 Athens, Greece. |
| May 13–17 | **Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.** |
| May 27–June 3 | Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461 |
| June 9–10 | Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium. |

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|---|---|
| June 12 | First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France. |
| June 13–16 | Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372 |
| June 24–28 | Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada. |
| July 10–13 | BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390 |
| September 9–11 | Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden. |

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

*British Journal of Urology* (1990), 65, 222–224
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# Book Reviews

**Urinalysis and Body Fluids.** A Self-instructional Text. Edition 2. By Susan K. Strasinger. Pp. xvi+221. Philadelphia: F. A. Davis Company. 1989. Price £19.38.

This is a detailed and beautifully illustrated book which should find a place in clinical laboratories regularly engaged in urine analysis or the examination of cerebrospinal fluid. More than half of the book is taken up with urine analysis. There is a good description of the function and diseases of the kidney followed by detailed chapters that lead the reader step by step through the physical, chemical, microscopic and more specialised tests of urine. Each chapter is preceded by a list of learning objectives which should have been achieved by the end of the chapter and study questions to enable the reader to check the material he has learned. The book is described as a self-instructional text and it fulfils that requirement admirably. The colour plates are breath-taking. This book is suitable for the medical laboratory technician in training, although medical students and others would also find much to interest them.

**Biliary Lithotripsy.** Edited by J. T. Ferrucci, M. Delius and J. H. Burhenne. Pp. xix+309. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price £61.00.

Since lithotripsy hastened the demise of open surgery for urinary calculi, we have been eagerly awaiting the technological advances that would similarly transform the management of biliary calculi. Although the title of this volume and the publisher's advertisements suggest that this has been achieved, closer perusal of the text reveals that we are still a long way from reaching that goal.

The book is compiled from the Proceedings of the First International Symposium on Biliary Lithotripsy held in Boston in July 1988. This brought together researchers, engineers and clinicians pursuing new modalities for non-surgical management oı cholelithiasis. The title is, therefore, a misnomer, since the book also includes sections on chemolysis with oral bile acids, solvent dissolution, endoscopic, mechanical and laser techniques. It is, in fact, a state-of-the-art update on alternatives to cholecystectomy.

It has been expertly compiled, divided into 12 sections covering topics ranging from the natural history of gallstones through laboratory and clinical studies to the logistics of implementing a lithotripsy service. Each section contains a series of concise presentations which are easily readable and well illustrated. While there is an underlying impression that this publication is aimed at convincing the American market of the benefits of lithotripsy, it still provides a reasonably balanced view of the therapies that are now available in the management of gallstones. Lithotripsy is beginning to emerge as a safe alternative to open surgery in a selected group of patients, but it cannot provide the answer to all of the problems posed by biliary calculi. At present, cholecystectomy still remains the therapy of choice for young patients and for those with poorly functioning gallbladders or complicated disease.

In such a rapidly evolving field, the information presented in this volume will obviously have a limited useful life, but it provides a fascinating update on a field which is of interest to so many diverse parties. At £61 it is unlikely that many clinicians will wish to purchase personal copies, but it should certainly be considered for most departmental libraries.

**Understanding Incontinence.** By Dorothy Mandelstam. Pp. xiv+79. London: Chapman and Hall. 1989. Price £5.95.

Dorothy Mandelstam's first book entitled "Incontinence—A Guide to the Understanding and Management of a Very Common Complaint" was published in 1977 and was a pioneer of self-help books for patients. This revised and renamed book presents a simple and brief summary of the nature of both urinary and faecal incontinence and how it might be managed, the emphasis being on self-help. The outstanding value of this book, however, is the wealth of practical advice which is offered, including not only every type of incontinence appliance but sections on toilet facilities for the disabled, details on social services and how to obtain financial support. There are comprehensive lists of advice centres, manufacturers, patient self-help organisations and books for further reading. This book, though a little over-priced at £5.95, can be confidently recommended by all doctors who come into contact with incontinent patients.

**Renal Disease. Classification and Atlas of Infectious and Tropical Diseases.** Edited by R. Sinniah, J. Churg and L. H. Sobin. Pp. xx+273. Chicago: ASCP Press. Distributed by Raven Press, New York. 1988. Price US$143.00.

This is the fourth volume prepared by the W.H.O. Collaborating Centre for the Histological Classification of Renal Diseases. Those familiar with the previous volumes, comprising glomerular, tubulo-interstitial, vascular and congenital diseases, will not be disappointed with this publication. The excellence of the atlases previously published in this series were in large measure due to the guiding influence of Drs Churg and Bernstein; this atlas is a worthy addition to those volumes.

The book under review is devoted to chapters on various infectious conditions—protozoal, worms, viral, bacterial, fungal, etc. Also included are chapters on diseases encountered in tropical climes as they affect the kidney, *e.g.* metabolic disorders, blood dyscrasias, snake bites, insect stings and so forth. The whole work is a mine of information which would be very difficult to obtain in a single volume elsewhere.

The worth of an atlas stands or falls by the quality of the illustrations, and it must be said that the colour photomicrographs are, almost without exception, quite superb. There are also many useful maps indicating the distribution of tropical diseases. However, this is more than just an atlas, for there is also a succinct and informative text. Anyone concerned with tropical and infectious diseases and their pathological effects on the kidney will be able to turn to this book with confidence and pleasure. The authors and publishers are to be congratulated on an outstanding publication.

**Voiding Function and Dysfunction. A Logical and Practical Approach.** By A. J. Wein and D. M. Barrett. Pp. viii+371. Chicago, London, Boca Raton: Year Book Medical Publishers. 1988. Price £28.50.

These days authoritative texts on controversial subjects tend to be exhaustive compendia of contributions from notable experts. Because this book was conceived, simply, as a contributory chapter to a larger text book (Adult and Paediatric Urology, edited by Gillenwater, Grayhack, Howards and Duckett), but grew and grew (371 pages), it is unusual in offering a consistent and non-repetitive discussion of a complex subject.

Part one presents an excellent detailed account of the anatomy, physiology and pharmacology of urine storage and voiding function. This section is very thorough and incorporates much of the historical perspective and controversy of the subject. Part two consists of chapters on urodynamics, the classification and management of voiding dysfunction. Discussions are included on specific neurological disease, urinary incontinence, bladder outflow obstruction and paediatrics. Where there is debate, this is clearly outlined and, despite professing their own allegiance to one school of thought or another, the result is a consistently balanced discussion which puts many previous "reviews" into a most revealing light.

The bibliography is, by any standards, long (865 references in all, with a few overlaps) and thus the text is necessarily cumbersome in places. One criticism, almost inevitable from this side of the Atlantic, is that the European literature is somewhat underrepresented. Nevertheless, for anyone interested in, or especially writing about, vesico-urethral function, this is a most valuable read.

**Nephrology.** Volumes I and II. Edited by A. M. Davison. Pp. xxxvii+1383. London, Philadelphia, Toronto, Sydney, Tokyo: Balliere Tindall. 1988. Price £60.00.

This book, which is in 2 volumes, is the Proceedings of the Xth International Congress of Nephrology held in London in July 1987. It is not a comprehensive textbook of nephrology but a substantial update of advances made throughout the whole spectrum of nephrology during the years 1984 to 1987. Although many of the papers record laboratory and research work, others are up-to-date reviews, and it is these that will prove of most interest to the urologist. It cannot replace the standard works on nephrology, but should certainly take its place alongside them as the information and references it contains are so up-to-date.

The editor, editorial board and publishers are to be congratulated on producing such an attractive and valuable book in such a short time and at such a low price.

**Genitourinary Ultrasound: A Text/Atlas.** Edited by Beverly G. Coleman. Pp. xviii+542. New York, Tokyo: Igaku-Shoin. 1988.

The quality of modern ultrasound is such that the images produced can approximate to anatomical diagrams, but to the uninitiated an act of faith is still required, particularly in poor subjects. Since ultrasound is a "performance art", requiring the operator to make up his mind on the spot, it is important for the beginner to know what he can expect to see and what he can infer from a less then ideal picture. Many atlases contain outmoded images or images that are badly reproduced, usually accompanied by simple diagrams in an attempt to clarify the situation. The unique feature of this book is its comparison of good ultrasound images with Hisako Kobayashi's excellent illustrations.

Each image is accompanied by an "idealised" schematic drawing of the image itself which clarifies the features demonstrated. These in turn are matched with a realistic anatomical diagram of the underlying anatomy and pathology. An informative text covering the pathology of the condition, including practical hints on technique and comparison with other imaging modalities, accompanies the illustrations. The emphasis is on large, clear pictures and a minor criticism is the amount of page-turning required to read the text as it relates to the pictures.

The opening section on normal anatomy and the common normal variants which can mislead is very informative. There follows comprehensive coverage of the ultrasound appearance of the kidneys, renal tracts, retroperitoneal structures, prostate and testes in health and disease. Both adult and paediatric practice is represented and there are sections on the transplanted kidney, interventional techniques and the intra-uterine diagnosis of renal anomalies. The relatively recent applications of doppler ultrasound for assessing renal transplants and rectal probes for examination of the prostate are included.

Although over 500 pages long, most of the space in the book is rightly taken up by the illustrations, making it highly readable. It would be at its most useful as a ready work of reference to dip into in the ultrasound room. Perhaps its greatest merit is the up-to-date nature of the real time images, since many texts lag behind clinical practice by the time they are published.

As a work for the radiologist in training, whether general or specialist, this book is hard to fault. It will also be of interest to the urologist as a demonstration of the scope of modern ultrasound. The sections on interventional techniques such as biopsy and drainage, and on the assessment of renal transplants, are particularly relevant to the surgeon. It is a reflection of the increasing scope of the modality that so much ground is now covered by only one system.

**Advances in Nephrology.** Volume 17. Edited by J.-P. Grunfeld, J. F. Bach, J. Crosnier, J.-L. Funck-Brentano and M. H. Maxwell. Pp. xxvii+442. Chicago, London, Boca Raton: Year Book Medical Publishers. 1988. Price: £53.50.

This is another excellent volume in the series started by the Department of Nephrology in the Necker Hospital, Paris, but now including an American editor and a strong transatlantic contribution which helps to provide a better balance. This is a very good collection of reviews on a number of topics which are of current interest in nephrology. This volume concentrates on glomerular pathophysiology in Part I and includes excellent chapters on the role of capillary hypertension in the pathogenesis of focal segmental glomerulosclerosis, glomerular haemostasis and diabetic nephropathy. Some of the chapters are controversial, for example that dealing with the treatment of idiopathic nephrotic syndrome in those patients who are resistant to steroids, and many chapters represent a personal point of view but are nonetheless well worth the effort to read.

Part II covers a wide range of subjects including lead nephropathy and calcium channel blockers in acute renal failure which are useful summaries of the current research and applications of this work to human disease. The section I found least satisfactory was the last. There were two lengthy chapters on pancreatic transplantation in which two groups described their current results and which sat oddly in this book. The chapters on hepatic complications in renal transplantation and on dialysis amyloidoses were excellent, although the references in the latter are inevitably out of date in such a fast moving field. This volume should find a place in any nephrology library.

**Genitourinary Trauma.** Edited by A. S. Cass. Pp. xi+298. Boston, Oxford, London, Edinburgh, Palo Alto, Melbourne: Blackwell Scientific Publications. 1988. Price £45.00.

The text comprises 298 pages, 17 chapters and involves 21 contributors. The major controversy in the treatment of trauma to the urinary tract is that of aggressive versus conservative management. The editor sets out in the foreword to present a balanced view, drawing opinions from both sides. In this he succeeds admirably. The text covers all forms of genitourinary trauma, both traumatic and iatrogenic, in both adult and paediatric populations.

There is a degree of re-duplication in the assessment and investigation of injuries by the various contributors. However, this does mean that a surgeon can confine himself to one aspect of the book if he so wishes. The contributors have in the main detailed their own experiences and each chapter is followed by an extensive bibliography.

The exposure to urological trauma in the average surgical practice is small. This book gives a "state-of-the-art" update, in a balanced manner. It can be thoroughly recommended both to trainee and experienced urological surgeons.

**Endocrine Therapies in Breast and Prostatic Cancer.** Edited by C. K. Osborne. Pp. xii+161. Boston, Dordrecht, Lancaster: Kluwer Academic Publishers. 1988. Price £37.95.

The rationale for considering the hormone manipulation of breast cancer and prostate cancer in the same volume is that both malignancies are susceptible to this approach to treatment. Unfortunately, the clinician managing breast cancer is not called upon to treat prostatic cancer and vice versa. This book, the latest in the series of cancer treatment and research, does provide an extensive and current review of the use of LHRH analogues, aromatase inhibitors, antioestrogens, antiandrogens and progestogens in the treatment of both malignancies. It is authoritative, well produced and reasonably priced. It provides an excellent comprehensive source of references and background for research workers in steroid biochemistry and surgeons in training (and their supervisors), embarking upon research or clinical trials with these agents.

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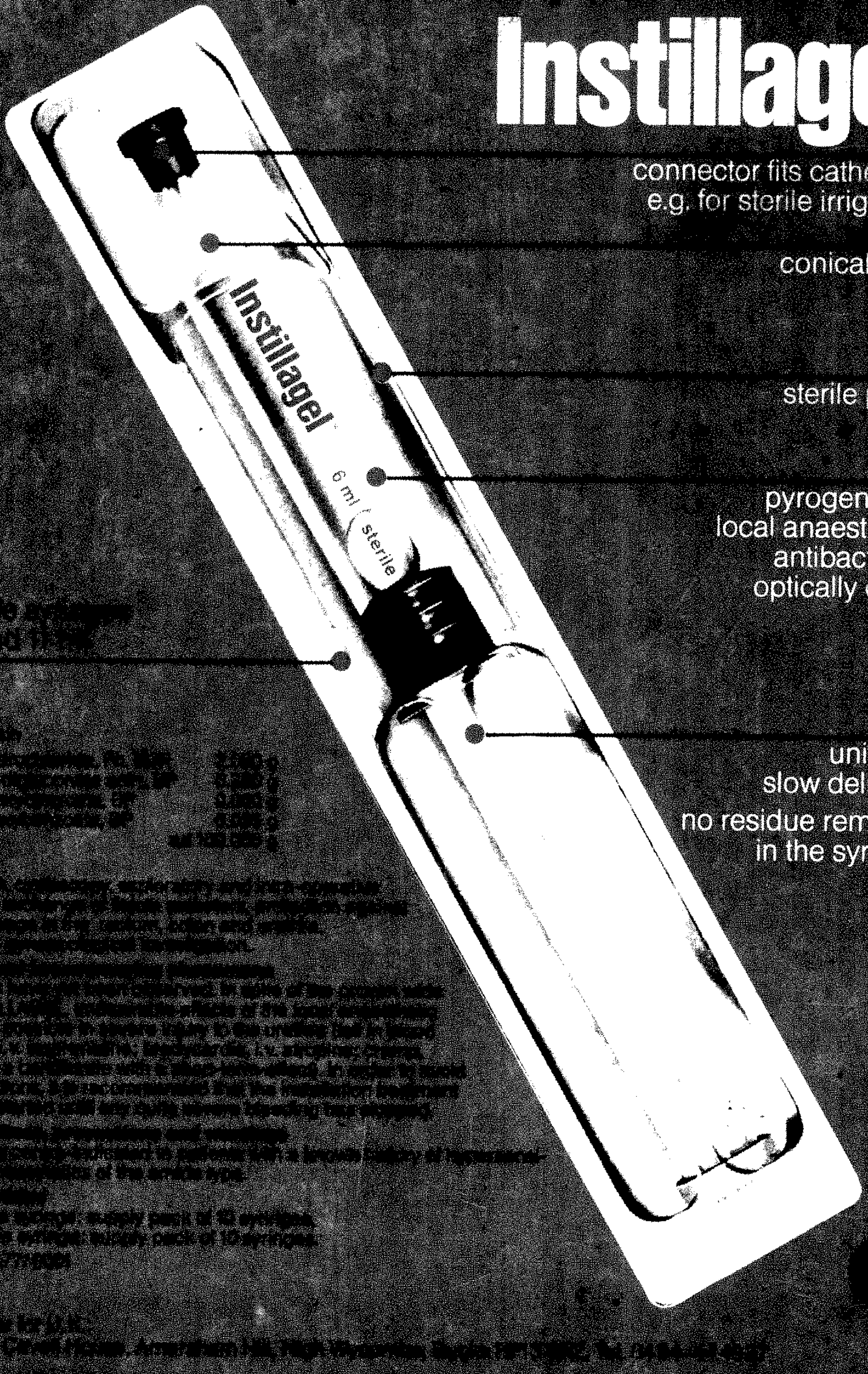

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**Manuscripts. Papers should be submitted in Journal style.** Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. **Two copies of the manuscript and illustrations should be submitted** and the author should retain a copy for reference.

**Authorship.** All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

**Original articles** should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The *title page* should give the following information: (1) title of article; (2) initials and names of each author; (3) the department and institution to which the work should be attributed.

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A list of 3 to 6 *key words* should be provided.

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*References.* The author is responsible for the accuracy of his references. When quoted in the text they should include the author's name and year of publication. In the case of 2 authors both names should be cited. If there are more than 2 authors, only the first author plus *et al.* should be quoted. The list of references at the end of the paper should be in alphabetical order and should give the names of *all* authors unless there are more than three, when only the first three should be given followed by *et al.* With journal references the following sequence should be observed: name(s); initials; date; title of paper; name of journal *abbreviated according to Index Medicus*; volume number; first *and last* page numbers. Thus:

**Morris, J. A., Oates, K. and Staff, W. G.** (1986). Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.*, **58**, 183–187.

References to books should be as follows:

**Wright, F. S. and Howards, S. S.** (1981). Obstructive injury. In *The Kidney*, ed. Bremner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

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*Tables* should be kept to a minimum and laid out as simply as possible. Each should be typed on a separate sheet, numbered in Arabic numerals and should not duplicate information in the text.

*Illustrations.* Photographs and radiographs should be submitted in the form of half-plate prints (approximately 17 × 11 cm). All figures should be unmounted. The number of the illustration (in Arabic numerals), the author's names, and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of photomicrographs and details of staining techniques should be given. Lettering on figures must be indicated on a transparent overlay. Illustrations in colour cannot be accepted unless the author is willing to cover the cost.

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**Proprietary names** of drugs, instruments, etc., should be indicated by the use of initial capital letters.

**Abbreviations and units.** All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors.*

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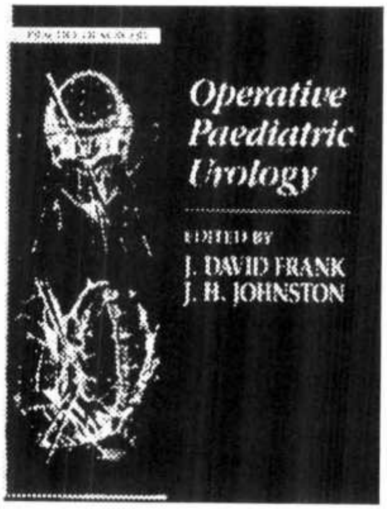

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# British Journal of Urology

Volume 66 No 6 December 1990

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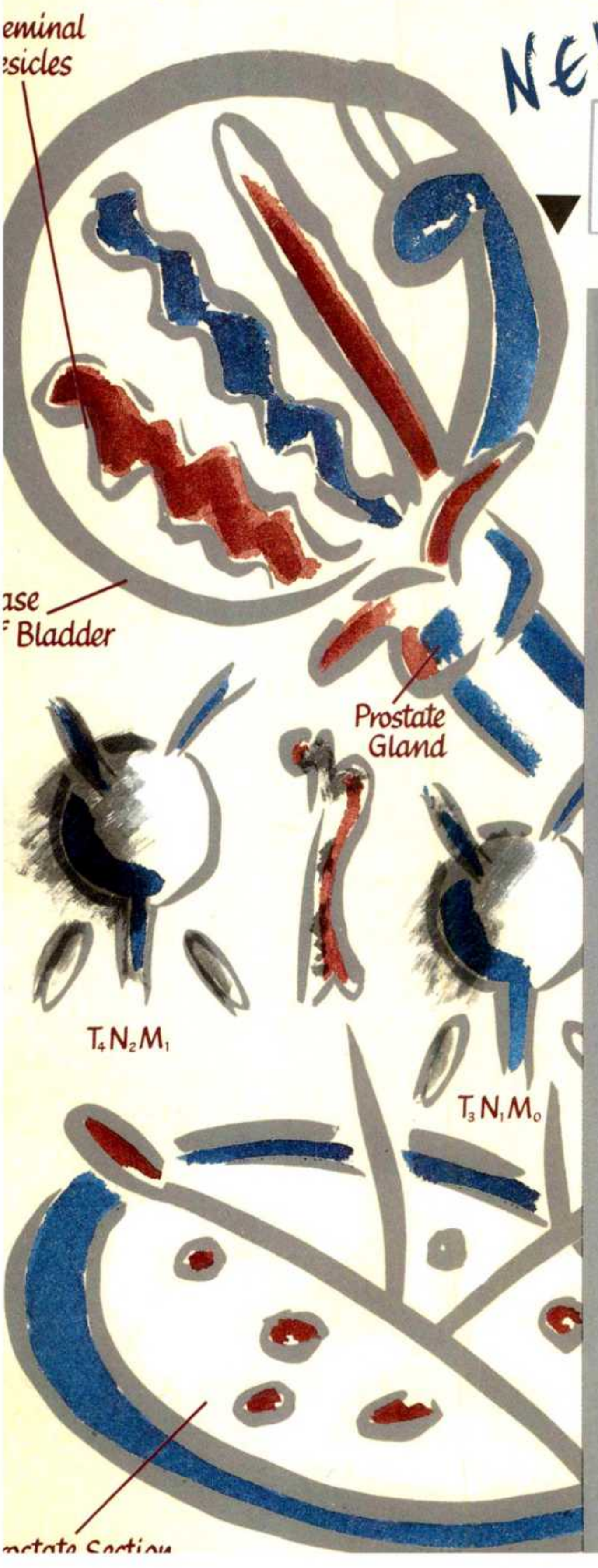

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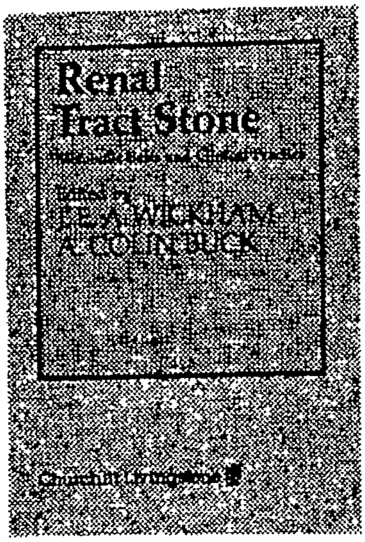

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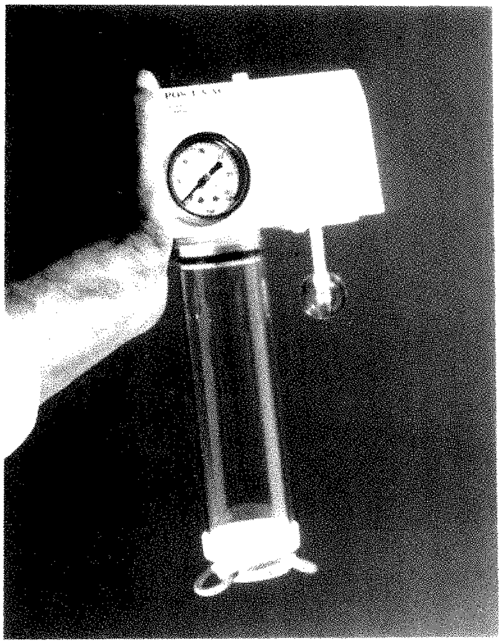

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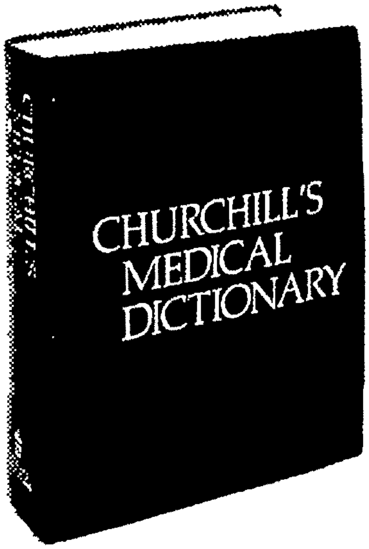

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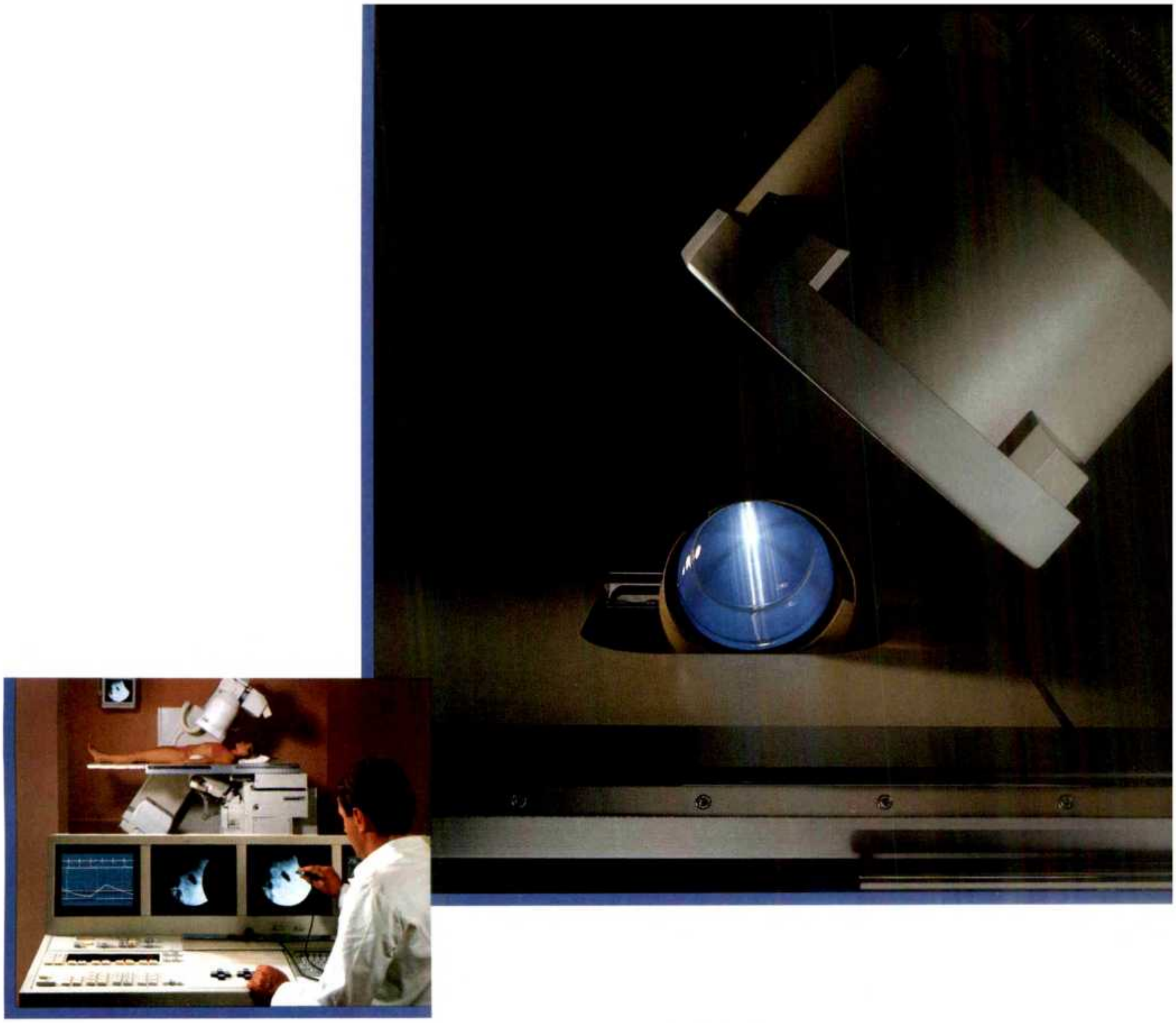

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| British Journal of Urology | 0007-1331 | 12 | January | |
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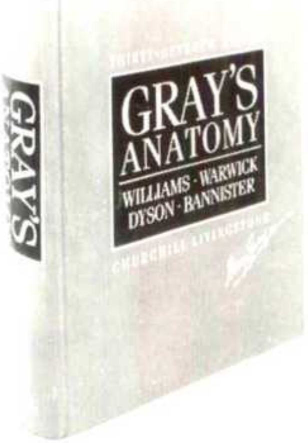

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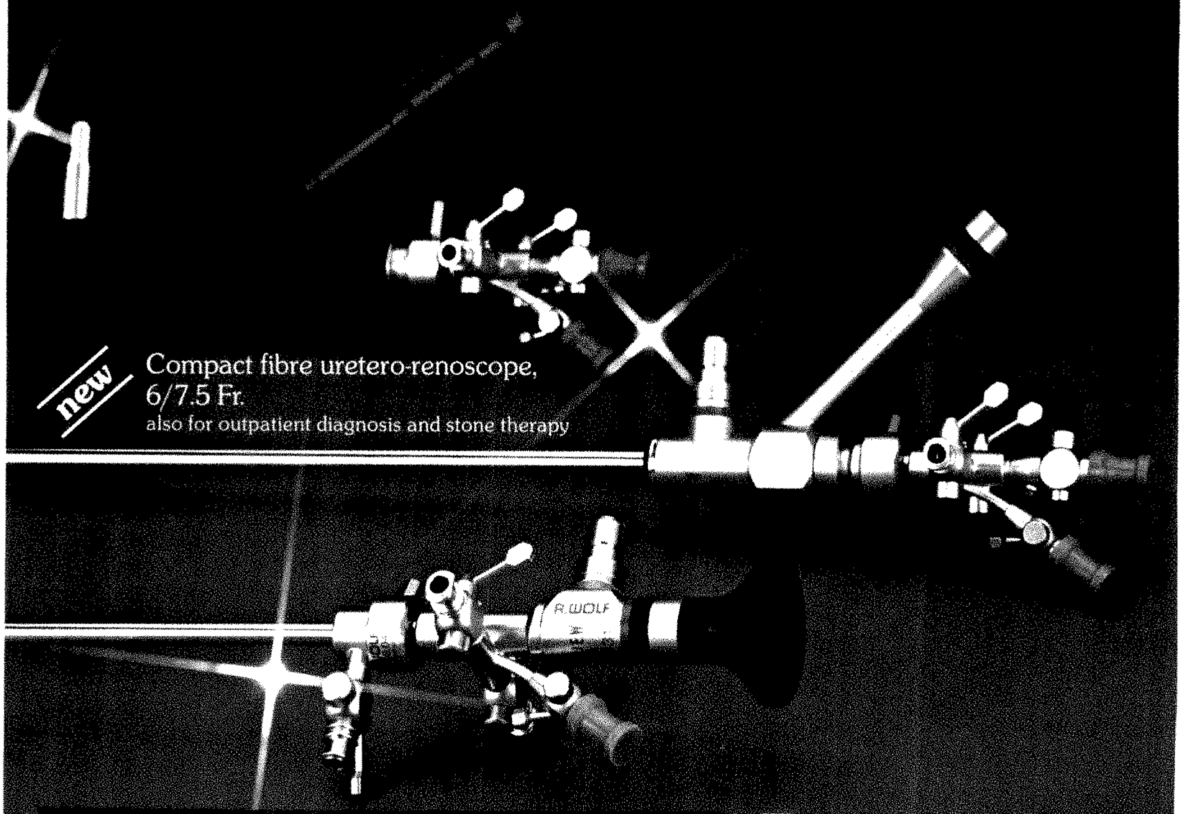

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REVIEW

# Intravenous Urography Revisited

P. DAWSON

*Department of Diagnostic Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London*

Intravenous urography remains the most frequently performed, contrast agent-enhanced procedure in diagnostic radiology. Newer contrast agents have made the procedure more comfortable and safer for patients, though at a significantly higher cost and with changes in the quality and pace of the examination. The historical development of this important technique is reviewed and the physiology of contrast agent handling, essential for understanding of image formation, is outlined. The problems of anaphylactoid reactions and contrast agent-associated nephrotoxicity are discussed and the place of the newer agents in this picture is indicated. Despite some dramatic developments in recent years of new technology and techniques of diagnostic imaging, such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound and isotope studies, the intravenous urogram (IVU) remains an important and simple means of visualising the renal tract. It has been performed for more than 60 years, during which time the chemistry of the essential contrast agents has changed and the sophistication and reliability of radiological and film technology have markedly improved but during which time the basic technique of the examination has remained unchanged. When carried out with the most modern of the contrast agents it is a safer procedure than ever before but should, of course, be used appropriately and always with a thought to the alternative techniques which may be available.

The interpretation of any radiological examination requires a knowledge of anatomy. Where the IVU is concerned, a full understanding of the images also requires some knowledge of physiology. This essential physiology will be discussed below.

## Historical Background

The first intravenous urogram was performed in 1923 at the Mayo Clinic by Osborne *et al.* (1923). These workers noted that the urine in the bladder was opaque to X-rays in some patients with syphilis who had been treated with large intravenous doses of sodium iodide. However, they had little success in obtaining good visualisation of the renal pelvis and sodium iodide was much too toxic to be administered in enormous doses.

It was some 5 years later that the first really successful IVU was performed using an agent of a type not too dissimilar to the agents of today (Fig. 1A). These were mono-iodinated pyridine compounds which had been synthesised, along with a large number of others, by Binz and Rath in Berlin in their search for an anti-syphilitic agent (Grainger, 1982). Some of the compounds were found to be not exclusively, but rather selectively, excreted in the urine ('Uroselectans') and in 1928/9 were used by a young American, Moses Swick, working in the Berlin department of the urologist, von Lichtenberg, to perform IVUs in animals and man (Marshall, 1977; Swick, 1978; Grainger, 1982).

Within 2 or 3 years these mono-iodinated pyridine compounds were replaced by more soluble versions, carrying 2 iodines and therefore offering a greater contrast punch (Fig. 1B). Because these agents were very effective they held sway until the early 1950s, when the tri-iodinated benzoic acid group of agents (also based on an idea of Swick) (Grainger, 1982) were introduced (Fig. 2). Just how good the second generation pyridine compounds were may be judged from Figure 3, which shows an IVU obtained in 1934 using one of them. When it is noted that this is a print of a copy of a copy of an old original from a time when radiograpic and film

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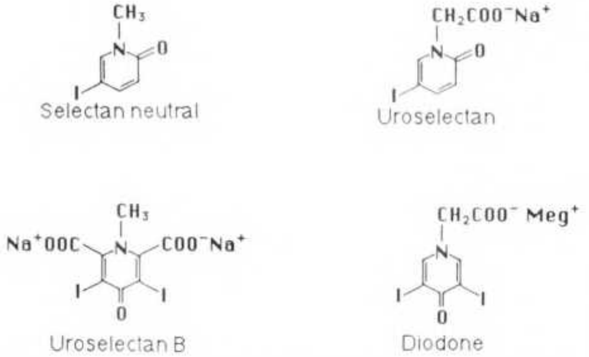


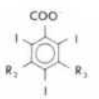
Selectan neutral

Uroselectan

Uroselectan B

Diodone

Fig. 1 (A) Mono-iodinated pyridine compounds used by Swick to perform the first IVU. (B) Diodinated pyridine compound successors of greater water solubility introduced in the early 1930s.



| $R_2$ | $R_3$ | Proper name | Commercial name |
|---|---|---|---|
| H | $NHCOCH_3$ | Acetrizoate | Urokon, Diaginol |
| $CH_3CONH$ | $NHCOCH_3$ | Diatrizoate | Urografin, Hypaque |
| $CH_3CONH$ | $CONHCH_3$ | Iothalamate | Conray |
| $CH_3CONH$ | $NCOCH_3$<br>$CH_3$ | Metrizoate | Isopaque, Triosil |

Fig. 2 The tri-iodinated benzoic acid derivative salts introduced in the 1950s. Still in use today, they are now known as the 'conventional ionic agents'.

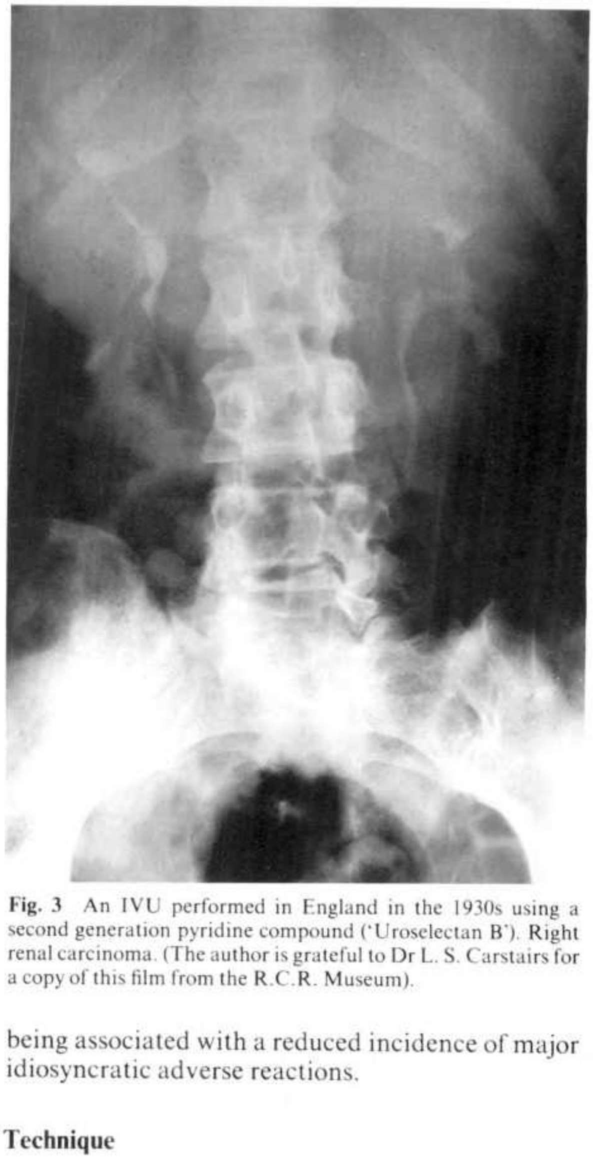


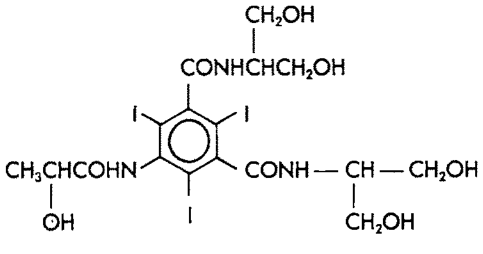
Fig. 3 An IVU performed in England in the 1930s using a second generation pyridine compound ('Uroselectan B'). Right renal carcinoma. (The author is grateful to Dr L. S. Carstairs for a copy of this film from the R.C.R. Museum).

technology were not what they are now, it will be realised how effective they were.

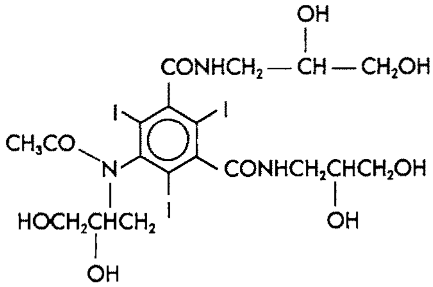
The benzene ring based agents introduced in the 1950s were a further distinct improvement both in terms of contrast density and tolerance, but these ionic agents were all of high osmolality—up to 7 times plasma osmolality—a fact responsible for some of their toxic effects. In recent years they have been superseded but not entirely replaced by a new generation of 'low osmolality' agents (Dawson *et al.*, 1983b). These are of 2 kinds, non-ionic and mono acid dimeric. The former are much better tolerated intravenously than either the earlier agents or the latter monoacid dimeric agents (Manhire *et al.*, 1984). Some non-ionic compounds are illustrated in Figure 4. These are not only associated with a reduced incidence and severity of subjective side effects than any other intravenous agents but are also significantly safer in terms of being associated with a reduced incidence of major idiosyncratic adverse reactions.

## Technique

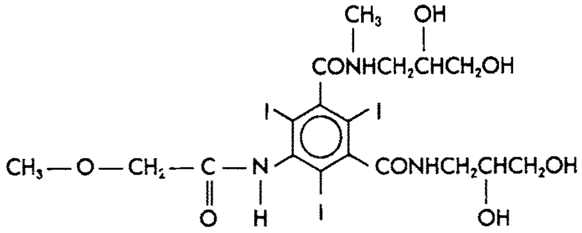
As indicated already, the basic technique of the IVU has changed very little since the subject was put on a rigorous scientific basis in the 1960s (Saxton, 1969). A bolus of an iodinated contrast agent is administered rapidly intravenously (typically ~ 300 mg iodine/kg body weight over ~ ½ min) and an 'immediate' film of the renal areas obtained (nephrogram phase). (In the past some radiologists preferred to give a slow infusion but this is now rarely done in Europe). More films are obtained of the renal areas at about 5 min to demonstrate the contrast-filled pelvicaliceal system (pyelogram phase). At about 10 min a full length abdominal film is obtained to demonstrate ureters and bladder



IOPAMIDOL



IOHEXOL



IOPROMIDE

**Fig. 4** The non-ionic 'low osmolality' contrast agents in use in the UK. Iopamidol (Niopam) (Merck), iohexol (Omnipaque) (Nycomed), iopromide (Ultravist) (Schering Health Care).

and finally, when appropriate, a post-micturition film of the bladder may be taken. Variations on the theme include tomograms when appropriate, administration of a diuretic to precipitate and demonstrate a pelviureteric junction obstruction, prone films and delayed films to try to demonstrate the level of an obstruction.

The review of Saxton (1969), though 20 years old and having nothing to say about low osmolality contrast agents, remains a key source of basic information on all aspects of the procedure. More recently, Hattery *et al.* (1988) have provided a technique update and Strautman *et al.* (1989) have investigated the possibility of performing *digital* intravenous urography, taking advantage of the high contrast sensitivity of such systems to use lower doses of contrast. Unfortunately, the latter authors found that no amount of post-acquisition image manipulation could compensate for the diminished image quality obtained using a low dose rather than a conventional dose of contrast agent. They did not use any low osmolality contrast agents in their investigation, leaving unanswered the question of whether some aspects of low dose digital IVUs might be adequate with low osmolality agents in view of the higher urinary concentrations these achieve (see below).

Traditionally, patients have been dehydrated prior to the examination in order to increase urinary contrast concentrations and pyelographic density. This is still widely practised but should be abandoned in view of its importance as a factor increasing the risk of nephrotoxic events associated with contrast agents (Dawson, 1985; Trewhella *et al.*, 1987; Dawson and Trewhella, 1990).

In summary, other than a greater range of choice of contrast media the technique remains essentially unchanged since the 1960s, and very little changed for half a century.

## Physiology and Contrast Handling

Following rapid bolus injection, iodinated contrast agents are rapidly diluted in the circulating blood volume and begin immediately to diffuse across the blood vessel walls into the extravascular extracellular space. The agents do not significantly enter the intracellular space. Within about 2 min some 70% of the administered dose has disappeared from the plasma. Strictly speaking, an equilibrium is never reached, for although distribution throughout the extracellular fluid space is very rapid, the plasma levels begin to fall immediately because of renal excretion. Contrast molecules are excreted by the kidneys entirely by passive glomerular filtration with no significant tubular secretion or reabsorption. The plasma half-life of contrast agents is of the order of 2 h.

*The Nephrogram*

The nephrogram is an essentially simple phenomenon. It represents X-ray absorbing iodinated contrast agent in the renal vasculature, in the extravascular extracellular space and in the proximal tubules. Radiographic density obtained in an 'immediate' nephrogram is a function of the total dose injected and the size of the patient.

*The Pyelogram*

The pyelogram is based on a more complex series of physiological events. If there is normal renal tubular function, 85% of water in the glomerular filtrate is reabsorbed from the proximal tubules. In the distal and collecting tubules more water is reabsorbed with further concentration of the urine, but this process is active and under the control of vasopressin. It is, of course, in order to increase the amount of absorption here that vasopressin levels have been traditionally raised in patients attending for IVU by dehydration. This should now be abandoned, as will be discussed below.

The presence in the glomerular filtrate of non-reabsorbable foreign molecules such as urea or contrast agent will engender an osmotic diuretic effect opposing the urine concentrating mechanisms. The osmotic effect will increase in accordance with the total dose of contrast agent (Fig. 5). As this dose increases, so does the amount of contrast material delivered into the urine. The osmotic diuresis increases and the urine concentration and pyelographic density therefore increase. However, at a certain dose level, the urine concentration reaches a plateau as the osmotic diuretic effect begins to dominate. After this point, pyelographic density cannot be enhanced further by any increase in contrast dose. With conventional ionic

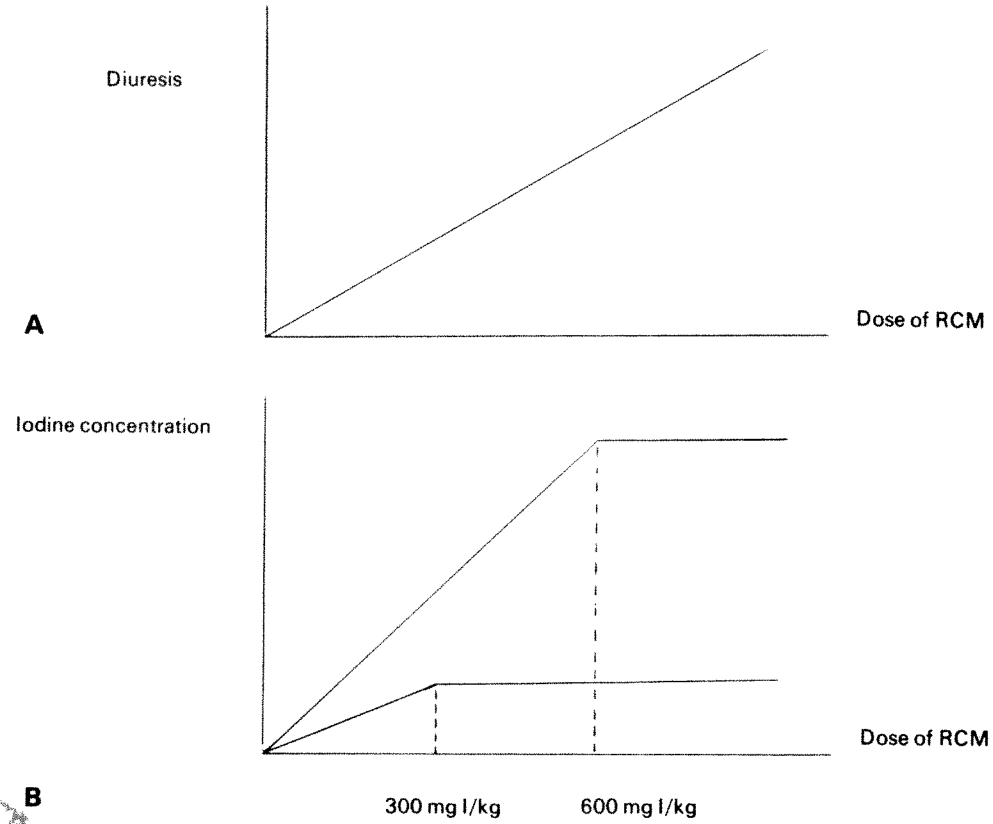


**Fig. 5** (A) The osmotic diuresis increases with increasing contrast load. (B) With increasing dose of contrast agent the urinary concentration and pyelographic density increase up to a point beyond which the osmotic diuresis dominates and a urinary iodine concentration plateau is reached. Concentrations are always higher for the low osmolality agents and the dose to achieve maximum is approximately twice as high because of their lower osmolality.

contrast agents the maximum pyelographic density is achieved with a dose of approximately 300 mg iodine/kg body weight (Saxton, 1969; Dawson *et al.*, 1984), this being the sort of dose which is given clinically in the UK for urography. However, with the low osmolality agents the diuretic effect, which is based on osmolality, is less marked and larger doses of contrast continue, to a higher level, to increase the urinary iodine concentration and therefore the pyelographic density. It is not until approximately 600 mg iodine/kg body weight that the plateau is reached (Dawson *et al.*, 1984).

Thus, for any given iodine dose administered, the low osmolality agents will produce higher urinary concentrations and pyelographic densities; they are also capable, in principle, for basic physiological reasons, of producing higher urinary concentrations and pyelographic densities than could be achieved by the conventional high osmolality agents at any dose.

A strong osmotic effect with a large osmotic diuresis will assist in the distension of the collecting system of the kidney, a desirable feature in an IVU. In the early days it was predicted that the low osmolality agents might produce a dense but rather poorly distended pelvicaliceal system with consequent loss of diagnostic information. However, at the iodine doses used in the UK and certainly with the use of abdominal compression, this anxiety has not been borne out in practice. However, it may be that there is a dose-dependent factor to be considered and if a low dose IVU is performed with a low osmolality agent there might, even with abdominal compression, be poor distension of the pelvicaliceal system.

Another consideration, predictable on simple physiological grounds, is that there will be slow filling of the bladder when the low osmolality agents are used, the reduced osmotic diuresis being responsible.

## Clinical Experience

The non-ionic agents have been in use in the UK for about 8 years. It was clear from the outset that they were better tolerated by patients and it was also realised that the IVU they produced was different in its details and in its style and pace, facts which are explicable on the basis of the analysis outlined above. Nephrograms appeared to be comparable, allowing for any difference in total iodine dose administered, but pyelograms seemed to be denser. At least when abdominal compression was used, there was no significant loss of pyelographic distension. These observations were first placed on a sound basis in a double-blind study by Dawson *et al.* (1984). The change of pace of the examination, arising from the lesser diuretic effect of the low osmolality agents, is seen in the relatively slow filling of the bladder. To the extent that the cystogram is an important part of the examination, it is a slower examination.

Other authors have made similar observations but with differences in detail and emphasis. Kay *et al.* (1988) found a difference in the pyelographic quality and density between 2 non-ionic agents but no simple explanation for this is readily to hand. Rawlinson *et al.* (1988) studied a large number of infants with a conventional agent and with 2 non-ionic agents. It was found that conventional ionic agent yielded slightly better nephrograms and pyelograms but the authors thought the differences had no significant effect on the information obtained. The explanation for this deviation from both theory and other clinical practice was not obvious but may be related to the lower dose used in children. It may be that there is a dose threshold which must be passed if good pyelographic density and distension are to be achieved.

## Safety of New Agents

Other than the general question of exposure to radiation, there are 2 significant problems associated with the IVU or, indeed, with any administration of an intravascular contrast agent. These are the severe (and occasionally fatal) iodiosyncratic adverse reactions to the agents (Ansell, 1970) and the nephrotoxic potential associated with them (Dawson, 1985; Dawson and Trewhella, 1990).

### *Anaphylactoid Reactions*

The mechanisms of these severe adverse reactions remain obscure, though a number have been postulated (Dawson, 1985). Perhaps the only thing which is clear is that most of them are not truly anaphylactic. There are some established risk factors, which will significantly increase the likelihood of such a major adverse reaction. These include previous reactions to contrast material, allergy to other materials, asthma, atopy and cardiac disease (Ansell, 1970; Grainger, 1984). Apart from the interesting matter of pathophysiology, however, a crucially important question is: are the non-ionic agents safer in this regard? Certainly the non-ionics are biologically more inert (Dawson, 1985), as is reflected in their greater tolerance, and so greater safety would not be too surprising.

Early evidence of their greater safety as compared to the conventional agents, in terms of a reduced degree of subclinical bronchospasm and a reduced number of electrocardiographic changes associated with their administration, was observed by Dawson *et al.* (1983a) and Heron *et al.* (1984).

The general impression in Europe was that the incidence of severe reactions was reduced with their use but it was felt that formal studies to establish this firmly would be difficult, if not impossible, to organise. This was because of the difficulty of controlling the very large scale multicentre trial which would be necessary and because a policy had been widely implemented of using non-ionic agents in all patients with definable risk factors on the working assumption that they were safer (Grainger, 1984). This would skew the data against the non-ionic agents; in addition, many radiologists would have misgivings from the ethical and medico-legal standpoint about giving conventional agents to any (control) patients who had definable risk factors.

In spite of such considerations, large scale studies have been performed in Australia (Palmer, 1988) and in Japan (Katayama *et al.*, unpublished observations). Both of these studies confined themselves entirely to intravenous injections of their conventional or non-ionic agents and so the results are directly relevant to the IVU. The Japanese data on 330,000 patients revealed an approximately 6-fold reduction in the incidence of severe and very severe reactions when non-ionics rather than conventional agents were used. The Australian data on 169,000 patients indicated a similar finding. In the groups definably at high risk there was a 12-fold reduction in the likelihood of a severe reaction in the Australian series. In both studies an interesting paradox emerged. If a patient was definably at high risk and therefore received a non-ionic agent, his risk level, on average, was lower than that of a patient with no definable risk factors who received a conventional ionic agent. In short, it is safer to have a risk factor (assuming you get the non-ionic)!

It seems clear that IVUs should be performed with a non-ionic agent since they are better tolerated by patients and because they are safer. However, they are substantially more expensive (5–6 times the cost of the equivalent conventional agent), a fact which has led to their being rationed in most centres, where they are reserved for the definably at risk patients only, in spite of the paradox inherent in this.

The medico-legal as opposed to ethical position in the UK appears to be that the use of a conventional agent for the IVU is defensible if no significant risk factors are definable in the patient. If such risk factors are definable, a non-ionic agent should be used.

There is no question but that in practice the threshold at which radiologists define 'increased' or 'definable' risk tends to slip and more and more patients are 'given the benefit of the doubt'. Despite financial restraints, some 40% by volume of all intravascular contrast agent used is now in the form of non-ionic agents. This represents more than 75% of the total expenditure. Although figures are not available, it appears that in intravenous urography the conversion rate to non-ionics has been less than the overall figure.

## *Nephrotoxicity*

An association between impaired renal function and administration of contrast has long been noted, but the mechanism remains obscure. This is an important issue in all centres where intravascular contrast is administered, but it is of special interest in intravenous urography where, by definition, many patients already have abnormal renal function. It is difficult to obtain hard data in this area and the literature is often confusing and contradictory. A recent editorial has attempted to distinguish between fact and assumption (Dawson and Trewhella 1990). The following can be stated as fact: many patients who receive intravascular contrast agents exhibit a transient rise in creatinine and fall in creatinine clearance; occasionally a patient may suffer acute-on-chronic clinical renal failure following a contrast examination; in animals and man, proteinuria (indicating renal injury) is seen following contrast injection, particularly after selective renal arteriography. No link has been established between the proteinuria and clinical events and no great significance seems to be attached to minor and short-lived changes in creatinine clearance. It appears that the risk of a significant clinical event is increased if the patient is dehydrated and/or receives a high contrast dose. Other alleged "risk" factors such as diabetes, pre-existing renal failure and old age have not been definitively established (Dawson and Trewhella, 1990).

Vasopressin release, stimulated by contrast administration, has been reported (Trewhella *et al.*, 1989). This is an osmolality-related phenomenon and is less marked with the 'low osmolality' agent. It is dramatically enhanced in the presence of dehydration. Since vasopressin is a potent vasoconstrictor, it reduces renal perfusion. It has been postulated that this may be one of the pathophysiological mechanisms of contrast agent-associated nephrotoxicity, an attractive hypothesis. It would suggest that the low osmolality agents should be safer in this regard, but it must be stressed that this has not been established. Some studies have found no clearcut difference between older and newer agents (Gomes *et al.*, 1989; Schwab *et al.*, 1989), but these are open to criticism and it must be concluded that the question remains open.

Whether or not vasopressin is involved in these important events, a consensus is emerging that dehydration should never be actively promoted and, if suspected, an attempt should be made to correct it before any contrast procedure. This is certainly the most important modification of established technique which needs to be reviewed.

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# Urological Complications in 350 Consecutive Renal Transplants

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Summary—Ten urological complications (2.9%) were found in 350 kidney transplants performed in this centre. These included obstructive uropathy (20%), urinary leaks (40%), distal uretic fistulas (necrosis) (30%) and renal calculi (10%). Two grafts were lost due to chronic rejection 9 and 30 months post-operatively. The remaining 8 patients have stable renal function (mean creatinine 1.5 mg%). It was concluded that meticulous surgical technique may reduce the number of urological complications and early diagnosis and prompt surgical treatment may help to save the grafts.

Urological complications in renal transplantation are important for several reasons mainly because the patients' immunosuppressive treatment leads to poor healing and a predisposition to local and systemic infection. During the first decade of renal transplantation, urinary fistulas occurred much more frequently (3–10%) than at present (Banowsky, 1983). They were particularly distressing not only because of their frequency but also because they were associated with high mortality rates and graft loss (25%). Transplant surgeons must aim to establish a watertight urinary system which has no parallel in standard urological surgery (Smith and Ehrlich, 1976; Salvatierra, 1986). Since urological complications may precipitate wound infection, septicaemia and death, early operative intervention is recommended.

## Patients and Methods

Between November 1975 and December 1988, 671 kidney transplant procedures were performed; 350 kidneys were transplanted into 346 patients (4 were second transplants). A total of 261 were from living related donors, 70 were from living unrelated (or second degree related) donors and 19 were from cadavers. Eleven patients who received kidneys from living related donors were ABO incompatible. Before transplantation, donor specific blood (DST) was administered (in 3 sessions at 10-day intervals; 150 ml each time without azathioprine) (Haberal, 1988) to 293 patients. Every patient underwent physical examination, laboratory studies, upper gastrointestinal radiography, abdominal ultrasound and cystography. Immunosuppressive therapy included cyclosporin-A 5 mg/kg/day (average), azathioprine 2 mg/kg/day and prednisolone 1 mg/kg/day. Prednisolone was adjusted to 20 mg/day just before the patient left hospital. Methylprednisolone (MP) was used for 3 days during rejection episodes. When rejection occurred despite this treatment, it was regarded as "steroid resistant rejection" and OKT-3 and plasmapheresis combination therapy were then carried out. Ureteroneocystostomy was performed by extravesical modification techniques (Lich *et al.*, 1961).

The bladder was drained with a 16 F Foley catheter and left for 3 days. Ureteric stents were used only when urological complications developed. The closed drainage system "Haemovac" was used for the wounds for 1 to 2 days. In the post-operative period, renal function was monitored clinically, biochemically and by using $^{99m}$Tc DTPA dynamic renal scintigraphy. Urological complications were detected by a combination of clinical features, deteriorating renal function, renal scintigraphy, ultrasound and percutaneous intervention.

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## Results

In our 346 living kidney transplant patients, 10 urological complications (2.9%) were observed (Table). Two obstructions were detected, 1 at the pelviureteric and the other at the vesicoureteric junction. Pyeloplasty was performed in the first patient, but the graft was lost 9 months after transplantation due to chronic rejection (Fig. 1). The second patient was admitted with pain due to a palpable mass on the graft side. Ultrasonographic examination showed marked hydronephrosis (Fig. 2). Initially, percutaneous nephrostomy was performed under ultrasonic guidance. Antegrade pyelography then showed a hydronephrotic kidney and vesicoureteric obstruction (Fig. 2). Graft function rapidly improved and pyeloureterostomy was performed 15 days later, using the patient's native ureter (Figs 3 and 4).

Leaks were found in 4 patients (1.2%). Open drainage was performed in 2 cases, ureterostomy in 1 and ureterouretostomy in the other (segmentary necrosis was the main pathology in this patient).

Three cases of distal ureteric necrosis (0.9%) were found; 1 was due to spermatic cord pressure and the other 2 were probably due to vascular deterioration of the distal ureter (Fig. 5). Extravesical neouretero-neocyctostomy was performed in all cases and all patients now have normal renal function (Table).

No surgical intervention was required in the patient with renal calculi (0.3%). Ultrasound revealed no obstruction, hydronephrosis or infection. When the calculi were diagnosed, the creatinine level was 2 mg/dl. It was therefore decided to wait until a fresh complication arose, but unfortunately the patient lost the kidney because of chronic rejection 30 months after transplantation. The 2 patients who lost their grafts returned to dialysis. The remaining 8 patients are progressing well and have stable, normal renal function.

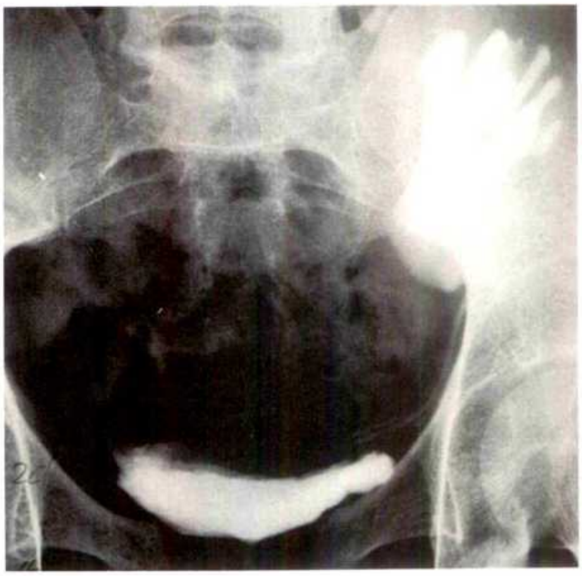

**Fig. 1** Pelviureteric obstruction and hydronephrosis after transplantation. Pyeloplasty was performed.

## Discussion

In this series, obstructive uropathy and urinary fistulas were the main cause of urological complications (Mundy *et al.*, 1981); Starzl *et al.*, 1970). The 2 urinary obstructions occurred at the pelviureteric and vesicoureteric junctions. Pyeloplasty was performed in the first case and pyeloureterostomy in the second. Intra-abdominal access was gained

**Table** Urological complications in 10 patients

| *Patients Name* | *Date of transplantation* | *Complication* | *Operation* | *Present graft function BUN/Cr % mgr* |
|---|---|---|---|---|
| H.K. | 14.3.1986 | Pelviureteric obstruction | Pyeloplasty | Graft lost 9 months later post-transplant |
| C.T. | 15.3.1986 | Renal calculi | — | Graft lost 30 months later post-transplant |
| Z.D. | 22.3.1986 | Distal ureteral necrosis | Ureteroneocystostomy | 25/1.2 |
| C.Y. | 30.7.1987 | Distal ureteral necrosis | Ureteroneocystostomy | 20/0.9 |
| A.K. | 12.2.1988 | Distal ureteral necrosis | Ureteroneocystostomy | 20/1.0 |
| S.G. | 5.4.1986 | Urinary leak | Ureterostomy | 50/3.0 |
| S.S. | 19.5.1986 | Urinary leak | Ureteroureterostomy | 40/2.5 |
| I.U. | 30.1.1987 | Urinary leak | Open drainage | 16/0.8 |
| B.E. | 16.10.1987 | Urinary leak | Open drainage | 20/1.0 |
| S.D. | 19.6.1987 | Vesicoureteric obstruction | Ureteropyelostomy | 30/1.6 |

through the transplant incision and renal function rapidly improved. Glass *et al.* (1982) performed a similar procedure in 7 patients with successful results. Rajfer *et al.* (1986) emphasised that when the transplant ureter was too small or too necrotic for re-anastomosis, pyelovesicostomy could be performed successfully. Our routine ureteroneocystostomy technique is extravesical mucosal anastomosis as described by Lich *et al.* (1961). This technique has a lower incidence of obstructions than the Politano-Leadbetter procedure (Starzl *et al.*, 1970; Mundy *et al.*, 1981). In the present study, 3 ureteric fistulas (necrosis) were diagnosed, due mainly to deterioration in the vascularisation of the ureter. In cadaver transplantation, this complication was seen more rarely because of the minimal hilar dissection (Smith and Ehrlich, 1976; Banowsky, 1983; Burdick, 1986; Salvatierra, 1986). To prevent this type of complication, ureteric dissec-

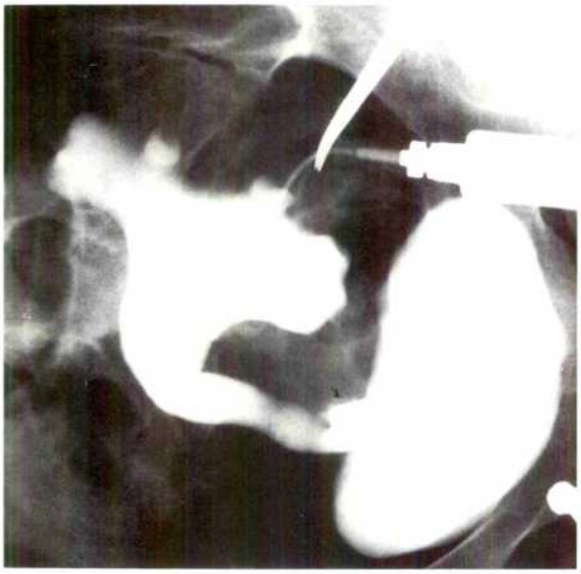

**Fig. 2** Vesicoureteric obstruction and hydronephrosis after transplantation showing percutaneous nephrostomy and antegrade pyelography.

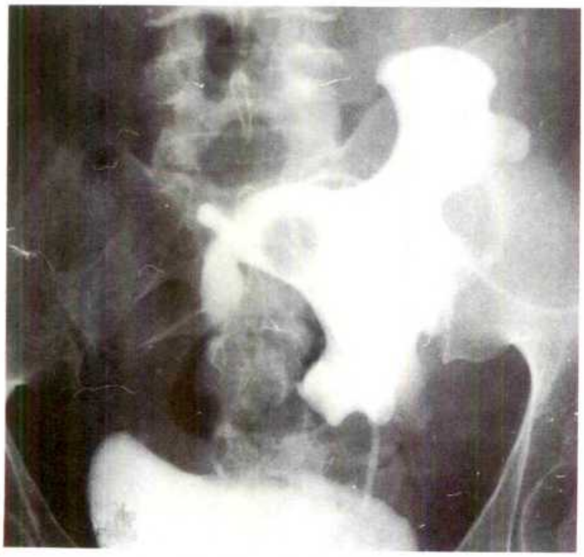

**Fig. 3** Vesicoureteric obstruction and hydronephrosis corrected by pyeloureterostomy using patient's native ureter; contrast dye passes freely to bladder.

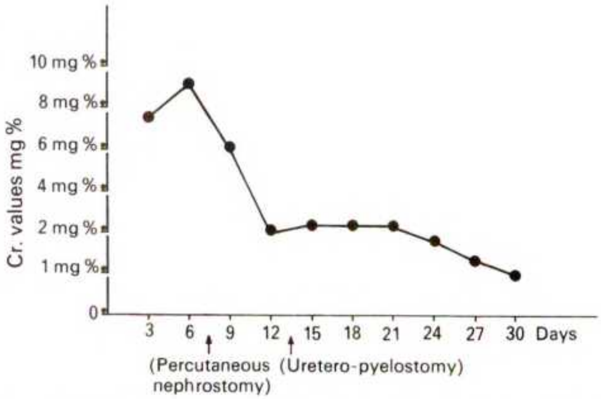

**Fig. 4** Kidney function had deteriorated markedly when the patient was admitted and returned to normal following percutaneous nephrostomy and ureteropyeloplasty.

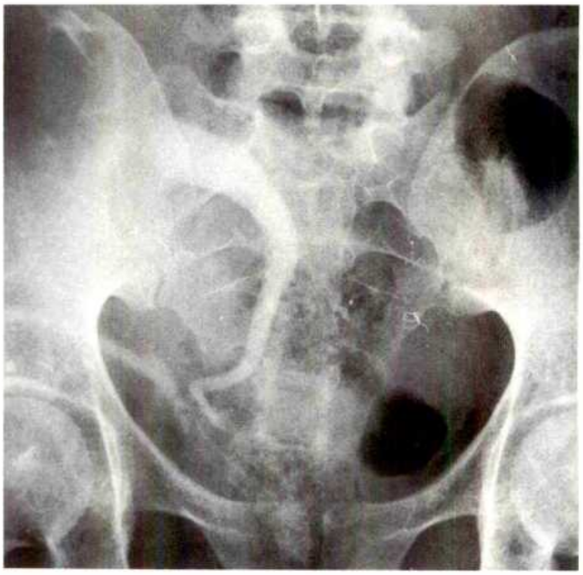

**Fig. 5** Ureteric fistula at vesicoureteric junction corrected by ureteroneocystostomy.

tion was performed with meticulous surgical technique. Spermatic cord dissection was one of the most important steps during recipient surgery. If cord dissection was insufficient, post-operatively ureteric obstruction might occur due to cord pressure, as happened in one of our patients. The cord was cut during surgery and ureteroneocystostomy was then performed.

In 1 of our patients a non-obstructive renal calculus was detected by ultrasound 18 months after transplantation. Since the creatinine value was 2 mg/dl, no further intervention was performed and the patient was monitored carefully by ultrasound. He eventually lost the kidney due to chronic rejection 30 months post-operatively. He eventually lost the kidney due to chronic rejection 30 months post-operatively. Streem *et al.* (1986) performed percutaneous nephrolithomy on the transplanted kidney stone but we were reluctant to embark on this procedure because we lacked sufficient experience. Urological complications may threaten the survival of both patient and graft and recurrent complications worsen the prognosis. Percutaneous techniques (Bennett *et al.*, 1986; Streem *et al.*, 1986) provide a definitive diagnosis but these procedures require subsequent operative intervention. We recommend that the appropriate intervention be performed as soon as possible because the intra-abdominal route may become easier using this procedure.

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# Emphysematous Pyelonephritis: Surgical Implications

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Summary—Emphysematous pyelonephritis in patients with diabetes mellitus is increasingly recognised as a disease requiring urgent and aggressive treatment. We present 3 cases of emphysematous pyelonephritis; 1 patient required percutaneous nephrostomy followed by nephroureterectomy but the other 2 were successfully managed with antibiotics and control of diabetes. Diagnosis was confirmed by sequential imaging techniques which demonstrated an inflammatory renal mass associated with gas and fluid.

The term "emphysematous pyelonephritis" refers to severe renal parenchymal infection with production of gas. This gas may be within the substance of the kidney or extend to the perinephric space or collecting system; 60 to 70% of cases are associated with uncontrolled diabetes mellitus, with or without obstructive uropathy and superadded infection with gas-forming organisms (Shultz and Klorfeni, 1962; Michaeli *et al.*, 1984). The initial high mortality rate has been considerably reduced by aggressive medical and surgical management, although not all patients require nephrectomy. We present 3 patients; 1 of these had a nephrotomy and 2 were managed successfully with antibiotics and control of their diabetes mellitus.

*Case 1.* A 55-year-old male was admitted as an emergency with left loin pain, dysuria and pneumaturia. Abdominal examination revealed a ballotable left kidney. A random blood glucose was 33·7 mmol/l. Urine examination showed gross glycosuria, proteinuria and pyuria. Urine culture grew *Esch. coli* sensitive to all antibiotics except ampicillin and nalidixic acid. Plain X-ray of the abdomen showed nephric and perinephric gas shadows with a central fluid-filled cavity with multiple fluid levels. Urography confirmed a non-functioning kidney (Fig. 1). There was a ureteric calculus obstructing the pelvic part of the ureter and gas in the ureter and bladder. Percutaneous nephrostomy yielded foul-smelling gas and pus which were extruded under great pressure; 600 ml of thick greenish blue pus were obtained and this grew a pure culture of *Esch. coli* similar to the urine culture. The patient responded dramatically and was given crystalline penicillin, gentamicin and metronidazole. His diabetes was controlled. Five days later a difficult nephrectomy was performed via a loin incision. There were dense adhesions to the peritoneum and diaphragm and the impacted ureteric stone was found in the lumbar ureter. The patient had a rapid recovery.

*Case 2.* A 60-year-old female diabetic presented with right loin pain, rigors and fever. She had a past history of

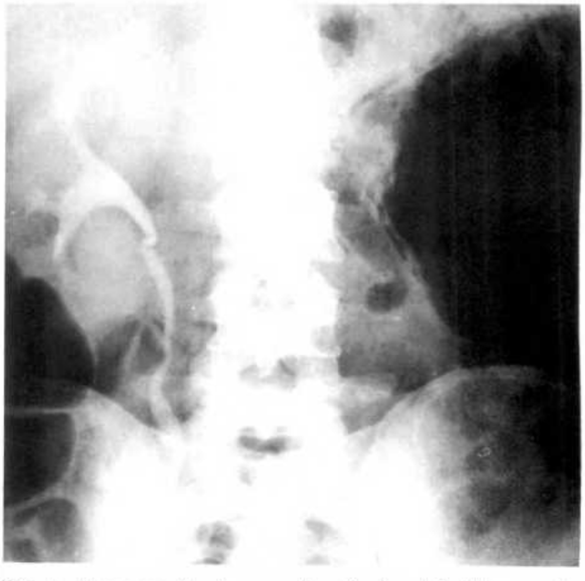

**Fig. 1** Urogram showing non-functioning left kidney with nephric and perinephric gas shadows.

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ischaemic heart disease, myocardial infarction and urinary tract infection. Examination revealed a toxic, acidotic patient with pyrexia of 39°C, a tender right loin and evidence of peripheral neuropathy. Haemography showed a polymorphonuclear leucocytosis. Her serum creatinine was 203 μmol/l, blood sugar 30 mmol/l and serum sodium 125 m Eq/l with a normal potassium. Her urine had an excess of WBCs and contained sugar and acetone. X-ray of the abdomen revealed no abnormality. Her diabetes was treated and ampicillin was commenced. Although her diabetes responded to treatment she continued to have a high temperature. Ultrasound examination of the upper abdomen, urography and computed axial tomography all suggested an inflammatory lesion of the right kidney. Urine and blood cultures showed a heavy growth of *Klebsiella pneumoniae*. There was right loin tenderness and fever 48 h after admission but repeat ultrasound did not show any marked difference from the previous picture. The patient continued to be very sick and toxic and cefotaxime (Claforan) was added to her regimen. This produced a drop in her fever 3 days later. Ultrasound examination (Fig. 2) showed a definite localisation of the inflammatory process to the upper pole of the kidney with air within the kidney which was confirmed on CAT scan. The patient was reluctant to have a percutaneous nephrostomy. The antibiotics were continued for 10 days with gradual improvement of her general condition. Serial ultrasound examination showed the air collection localised to the upper pole of the kidney, followed by a fluid level with air (Fig. 3). Resolution occurred 30 days from the onset of the symptoms.

*Case 3.* A 60-year-old female diabetic presented with left loin pain, fever of 40°C, blood sugar 35 mmol/l with normal electrolytes. She had had a myocardial infarction 1 month before admission. Her urine was loaded with pus cells. Urine and blood culture produced a heavy growth of *Esch. coli*. She was commenced on amikacin (Amikin) and pipracillin. Ultrasound and CT scan showed an inflammatory mass in the kidney. After 7 days' treatment with antibiotics she still had a fluctuating temperature. Amikin was discontinued and cefotaxime was instituted. Two days later her temperature peaks were reduced and 4 days later her fever subsided. Serial ultrasound imaging showed the inflammatory mass progressing to gas and fluid formation in the upper pole of the kidney. As her clinical picture was greatly improved this was not aspirated. Ultrasound imaging of the kidney every 4 days showed the inflammatory mass, gas and fluid resolving with a concomitant improvement in her general condition. Antibiotics were continued for a total period of 19 days. Urogram 1 month after admission showed function in this kidney.

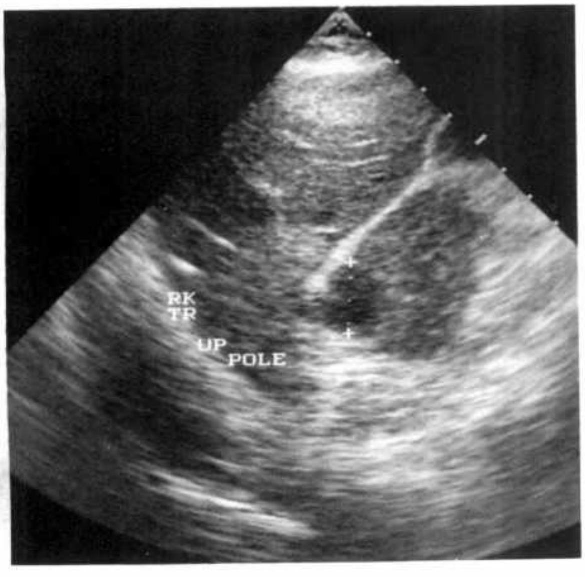

**Fig. 2** Ultrasound examination showing inflammatory process localised to upper pole of kidney.

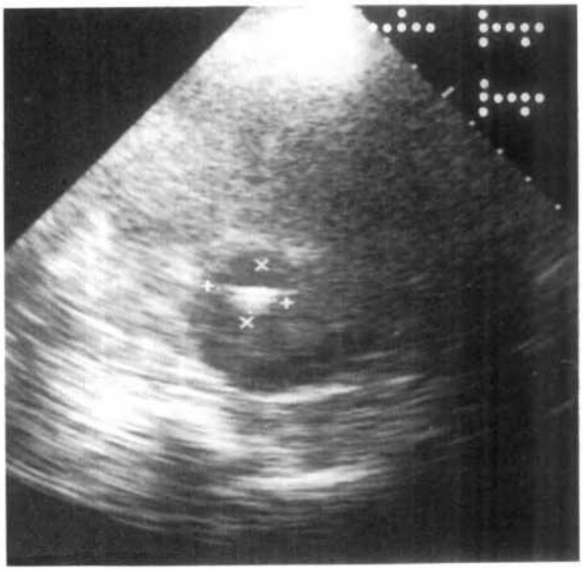

**Fig. 3** Ultrasound examination showing air and fluid level localised to upper pole of kidney.

## Discussion

Gas formation in the urinary tract associated with urinary tract infection is life-threatening. Kelly and MacCallum (1898) reported the first clinical observation of gas-forming infection in the kidney (Schultz and Klorfeni, 1962; Stokes, 1966). The gas was demonstrated by ureteric catheterisation and subsequent drainage of an infected kidney. The first radiological diagnosis of renal emphysema was made by Randall (Schultz and Klorfeni, 1962; Stokes, 1966).

In emphysematous pyelonephritis there is severe renal infection and gas in the renal parenchyma, collecting system or perinephric space. The patient invariably has uncontrolled diabetes mellitus and may have associated obstructive uropathy; 75% of patients have *Esch. coli* urinary tract infection but *Proteus, Pseudomonas, Klebsiella* and *Aerobacter* organisms have also been identified. *Candida albicans* infection was reported by Johnson *et al.* (1986).

Pyelonephritis in a diabetic kidney associated with renal ischaemia results in a low oxygen tension which induces anaerobic metabolism. Organisms such as *Esch. coli, Proteus mirabilis* and *Klebsiella pneumoniae* are facultative anaerobes and are able to ferment glucose to lactate and carbon dioxide. Schainuck *et al.* (1968) reported that carbon dioxide is the gas responsible for the appearance on X-ray examination.

The management of emphysematous pyelonephritis is controversial. Nephrectomy has been the treatment of choice (Michaeli *et al.*, 1984; Ahlering *et al.*, 1985). This is because of the high mortality rate of conservative management. Even with immediate nephrectomy, Ahlering *et al.* (1985) had a mortality rate of 42%. They recommended that all diabetics hospitalised with urinary tract infection or pyelonephritis should have a plain film of the urinary tract. If this was normal and the patient deteriorated or showed no improvement on appropriate antibiotics, a CT scan should be done to exclude emphysematous pyelonephritis, renal abscess or perinephric abscess with or without urinary obstruction. The patient should then be prepared for nephrectomy, which may not be easy.

Diabetes mellitus and urinary tract disease are common entities in Kuwait. In the past, septicaemic patients who failed to respond to antibiotics for severe renal infections required exploration for a clinical diagnosis of pyonephrosis. This exploration identified renal cortical abscesses which were drained. The clinical findings in our patients are similar to those reported in the literature (Michaeli *et al.*, 1984). In uncontrolled diabetic patients who present with high fever and inflammatory renal masses which are slow to respond to antibiotics and progress to intrarenal or extrarenal gas formation, we perform a plain film of the kidneys, ureters and bladder to document parenchymal or perinephric gas. If doubt persists, we perform CT of the abdomen without contrast material. Ultrasound imaging has also been useful.

Initially our principles of management were similar to those of Ahlering *et al.* (1985) and we performed nephrectomy. Our 2 subsequent patients were unsuitable for surgery because of recent myocardial infarction and we were encouraged by a report by Hudson *et al.* (1986) of successful percutaneous management of emphysematous pyelonephritis. We followed these 2 patients very closely with sequential CT scans and are pleased to report a successful outcome.

We agree with Ahlering *et al.* (1985) that poor blood flow is associated with the diabetic kidney, especially one with emphysematous pyelonephritis, which inhibits antibiotic perfusion to the kidney. The entire kidney is involved and there is no sparing of renal parenchyma to allow for partial nephrectomy. Thus it is concluded that although nephrectomy may be required, there is a place for conservative management with every chance that there may be recovery of renal function.

## Acknowledgement

We are grateful to Mrs Leela Varghese for secretarial services.

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# Excretion of Urinary Protein Induced by Extracorporeal Piezoelectric Lithotripsy

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Summary—An investigation was carried out into renal injury caused by extracorporeal piezoelectric lithotripsy (EPL) using an EDAP lithotriptor. Four urinary proteins, with a molecular weight range of 160000–14500, immunoglobulin G (IgG), N-acetyl-beta-glucosaminidase (NAG), albumin and lysozyme, were monitored in 27 patients 1 day before and 1, 7, 30, 90 and 180 days after unilateral EPL treatment. All patients had non-obstructive renal stones, previously untreated. Apart from 5 patients with stablised hypertension and 6 with persistent urinary infections due to the infected stones, all patients appeared healthy, as confirmed by clinical, haematological and biochemical investigations. Only albumin levels increased significantly 1 day after treatment; statistically non-significant increases and decreases were recorded in the levels of NAG and lysozome respectively. IgG was beyond the limit of detection (<0.5 mg%) in all patients. The albumin level returned to normal 7 days after treatment. The EPL-induced increase in albumin was recorded in 88% of patients, compared with increased levels of NAG in 46% and lysozyme in 64%, mainly in those with infected stones. These findings indicated a transient glomerular injury after EPL treatment.

In 30% of patients with urinary calculi (2–3% of the adult population in the USA) (Atala and Steinbock, 1989), urological intervention is required. ESWL or EPL, a non-invasive technique of fragmenting urinary stones by using shockwaves, was introduced in 1980 in Germany and in 1984 in the USA as alternative treatment. The first generation Dornier lithotriptors employed fluoroscopy of calculus imaging and electrohydraulic shockwaves for disintegration. The second generation piezoelectric lithotriptors incorporated several improvements: localisation of stone by ultrasound, thereby avoiding exposure to X-rays, concentration of the energy of shockwaves (produced by piezoelectrically activated ceramics) into a focus, which enabled pain-free treatment, and coupling of a soft rubber bag containing water with the patient, which eliminated the necessity for immersion in a water bath (Chaussy and Fuchs, 1989; Kiely *et al.*, 1989; Kim *et al.*, 1989). The rapid acceptance of ESWL was facilitated by its perception as an entirely safe treatment devoid of side effects. Now, however, there is abundant evidence to show that ESWL can cause severe side effects, including gross haematuria (Donahue *et al.*, 1989; Finlayson and Ackermann, 1989; Gunasekaran *et al.*, 1989), intraparenchymal and perirenal haemorrhage (Abrahams *et al.*, 1988; Lingeman *et al.*, 1989), transient increases in serum and urinary values of bilirubin lactic dehydrogenase, glutamic oxaloacetic transaminase, creatine-phosphokinase, NAG, $\beta$-galactosidase and $\gamma$-glutamyl transpeptidase (Ackaert and Schroder, 1989; Assimos *et al.*, 1989; Haupt *et al.*, 1989). In spite of the almost unanimous conclusion that shockwaves have short-term physiological effects on renal function and focal histological effects that do not affect long-term physiological function (Gilbert *et al.*, 1988; Graff *et al.*, 1988), EPL may cause chronic changes such as hypertension, decreased renal function or an increased rate of stone recurrence (Finlayson and Ackermann, 1989). Most of the studies on the harmful effects of ESWL were

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performed using the first generation lithotriptors and there is little information on renal injury caused by the second generation lithotriptors, which use higher numbers of shockwaves: for stones measuring 1 cm in diameter, the EDAP LT.01 (using 100% power, frequency 2.5 Hz in 40 min) uses 6000 shocks (Kiely *et al.*, 1989) compared with standard first generation lithotriptor treatments using 500–3000 shock waves (Haupt *et al.*, 1989).

We monitored 4 urinary proteins before and at various intervals for 6 months after EPL, using an EDAP LT.01 lithotriptor, to see if the treatment caused renal injury.

## Patients and Methods

Thirty patients with symptomatic renal calculus disease (17 men and 13 women), previously untreated, participated in the study. Their mean age was 49.8 years (range 19–80). Five individuals had hypertension controlled by medical therapy. Six patients with persistent urinary infections (5 due to *Klebsiella pneumoniae* and 1 to *Proteus mirabilis*) were treated with appropriate antibiotics before EPL. All patients underwent clinical, haematological and biochemical studies 1 day before and 1, 7, 30 days and 6 months after treatment. Three patients who failed to attend for follow-up were excluded. All calculi were radio-opaque and lay in the renal pelvis or calices; they measured between 0.8 and 2.0 cm. Fifteen apparently healthy persons (24–69 years of age), with no history of medical or urological problems, served as controls.

Each patient was treated with the EDAP LT.01 (Edap International Co., Croissy Beaubourg, France) lithotriptor for 50 min (100% power, frequency 2.5 Hz, *i.e.* 6000 shocks), with the power of the shockwaves gradually increasing over the first 5 min. In 12 patients the procedure was painless, but the others received an opiate analgesic.

Follow-up consisted of haematological tests: counts of white and red blood cells, haemoglobin, haematocrit by a Technicon H-I System (Tarrytown, USA); serum biochemical measurements: glutamic oxaloacetic transaminase, glucose, creatinine, urea, alkaline phosphatase, cholesterol phosphor, uric acid, calcium, sodium and potassium by an SMA II (Technicon Instruments Corporation, Tarrytown, USA); general urinary studies: leukocytes, nitrite, pH, protein, glucose, ketone, urobilinogen, bilirubin, erythrocytes by Conbur/Urotron RL9 (Boehringer, Mannheim, FRG), and other investigations: IgG, NAG, albumin, lysozyme and bacteriological culture of the urine. Early morning voided urine specimens were centrifuged at 1500 g for 10 min, filtered through 0.45 μm Ministart filters (Sartorius) and then stored for a maximum of 1 week at 4°C (Erman *et al.*, 1988; Giampietro *et al.*, 1989). IgG concentration was determined in 5 × concentrated urine by Lyphogel (Gelman Sciences—catalogue no. 48106) by a radial immunodiffusion technique (Johnson, 1986) using anti-human IgG (Kallestad, catalogue no. 204). Albumin was determined by Microalb Urin-pak immuno (Ames Division, Miles Laboratories Ltd, Stoke Poges). Briefly, when human albumin reacts with its specific antibody, precipitating immunocomplexes are quickly formed in the presence of polyethylene glycol. If the antibody is in excess, these precipitates produce turbidity which is related to the concentration of albumin in the sample. The turbidity is photometrically measured at 340 nm and the concentration of albumin is derived from a calibration curve obtained by a set of calibrators. The assay range was 5 to 160 mg/l; the intra- and inter-assay coefficients of variation were 7.9 and 9.3% respectively. NAG concentrations were determined by a spectrophotometric assay (Horak *et al.*, 1981): urine was filtrated by Sephadex G-25 (Pharmacia, Uppsala, Sweden) to remove enzyme inhibitors and the product of hydrolysis of p-nitrophenyl-N-acetyl-D glucosaminide at pH 4.4; the p-nitrophenylate was spectrophotometrically measured at 405 nm. The urine NAG activity test had a range of 0 to 30 u/l with a precision of 5.3 and 8.9% in intra- and inter-assays respectively. Lysozyme concentrations in urine were performed after adaptation of previous *Micrococcus lysodeikticus* lysis assays (Harrison *et al.*, 1968; Horpacsy *et al.*, 1978; Urivetsky *et al.*, 1989) to a microplate kinetic enxymatic assay. Briefly, to microplate wells containing a 200 μl fresh suspension of *Micrococcus lysodeikticus* (625 μg/ml) (Sigma Chemical Co., London, catalogue no. L-6876), 40 μl containing cyrstalline egg white lysozyme (Sigma Chemical Co., London, catalogue no. M-3770) dilutions of urine were added and the absorbance was recorded kinetically every 10 min at 450 nm. The limit of detection was 0.1 μg lysozyme/ml with a precision of 10.3 and 12.4% in intra- and inter-assays respectively. All measurements were expressed as fractions of the respective urine creatinine value (Lemann and Doumas, 1987).

## Results

Thirty patients with urinary stones were evaluated haematologically and biochemically after EPL. Of the haematological measurements, only the RBC and haematocrit showed a non-significant transient decrease ($P > 0.1$). There were no significant changes in the biochemical measurements. One day after treatment, all urine samples showed microscopic or macroscopic haematuria. The creatinine clearance of those patients was 83.6 ± 26.6 ml/min before treatment and 83.8 ± 27.7 ml/min afterwards.

IgG was <0.5 mg/mmol creatinine in both controls and patients (Table). Albumin, NAG and lysozyme were slightly elevated in patients before treatment compared with the controls ($P > 0.1$). Six months after treatment, the mean level of albumin was similar in patients and controls, while NAG and lysozyme remained slightly elevated in the patients. Only the albumin level increased significantly 1 day after treatment (Fig.) ($P < 0.005$). A slight, non-significant increase in urinary NAG was observed after treatment. In 88% of the patients, EPL was followed by an increase in albumin (Fig.) compared with only 46 and 64% of patients with increased levels of NAG and lysozyme respectively. Seven days after treatment, the levels of albumin decreased in 89% of the patients compared with 31 and 53% of patients with decreasing levels of NAG and lysozyme respectively.

## Discussion

The side effects of ESWL for renal lithiasis include haemorrhage, oedema, tubular necrosis and fibrosis of the kidney (Ackaert and Schroder, 1989). Apart from the morphological changes, changes in renal function were investigated by several authors. Since we found no data on the renal injury induced by lithotripsy with the EDAP LT.01, we investigated the excretion of certain renal proteins after treatment with this lithotriptor. Two main short-term changes in blood and urine follow lithotripsy: dilution due to the related infusions and cellular injury due to the high energy treatment (Haupt *et al.*, 1989). Measurement of daily urinary protein excretion and urinary creatinine to ensure completeness of the urine collection are commonly used in the diagnosis and follow-up of patients with kidney diseases (Lemann and Doumas, 1987).

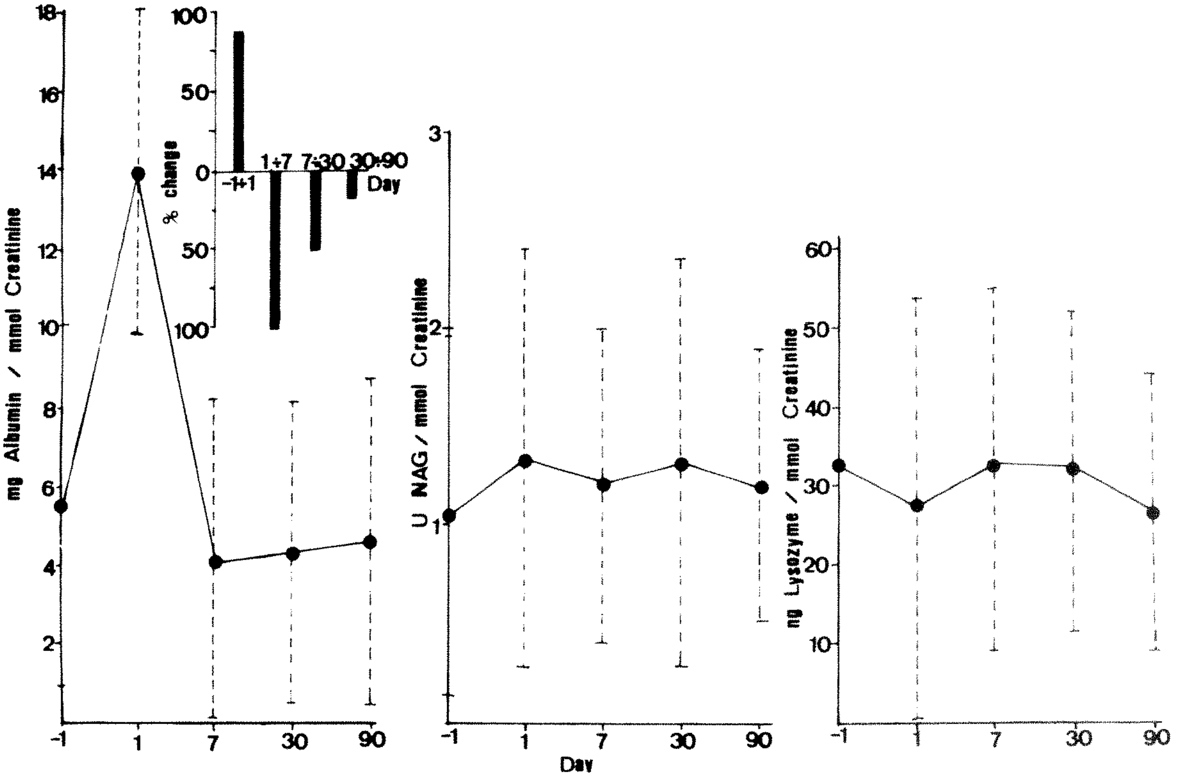

**Fig.** Mean albumin, NAG and lysozyme levels (±SD) per mmol creatinine before EPL (negative days) and after EPL (positive days). Insert shows percentage of patients with increasing or decreasing albumin levels between −1 and 1 day, 1 and 7 days, 7 and 30 days and 30 and 90 days.

**Table** Urinary Protein Excretion due to Extracorporeal Piezoelectric Lithotripsy

| | | | *Days after treatment* | | | | |
|---|---|---|---|---|---|---|---|
| | *Controls* | *Before treatment* | *1* | *7* | *30* | *90* | *180* |
| IgG (mg) | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 |
| NAG (u) | 0.83±0.61 | 1.05±0.90 | 1.33±1.10 | 1.19±0.78 | 1.27±1.05 | 1.15±0.69 | 1.14±0.63 |
| Albumin (mg) | 4.93±2.30 | 5.48±4.60 | 14.02±6.62* | 4.10±4.10 | 4.44±3.6 | 4.62±4.0 | 4.89±3.91 |
| Lysozyme (ng) | 29.89±10.17 | 32.4±29.52 | 27.44±27.01 | 32.78±23.65 | 32.5 ±21.81 | 32.9 ±24.06 | 33.1 ±20.21 |

$^*P<0.005$, significantly different from value before treatment.
Mean (±SD) per mmol urinary creatinine

Assessment of the type of urinary protein is useful in the differentiation of glomerular and tubular causes of proteinuria. The passage of molecules across the glomerular border is a function of molecular size, charge and configuration (Waller *et al.*, 1989). Thus proteins with a relative molecular mass >40,000 Da are almost completely retained, while smaller substances easily enter the glomerular ultrafiltrate; albumin, with a molecular mass of 69,000 Da and a negative charge at physiological pH, is almost completely restricted by the glomerular capillary wall. Polycations in the serum, such as lysozyme, readily penetrate the glomerular capillary wall. Most of the proteins in the glomerular filtrate are reabsorbed by the proximal tubular cells in which they are digested by enzymes. We used IgG and albumin to monitor glomerular function and NAG and lysozyme in order to determine tubular function.

Quantification of urinary albumin excretion (Magnotti *et al.*, 1989) is often used for the early assessment of lesions of the glomerulus in pathological conditions such as essential hypertension (Marre *et al.*, 1987), kidney rejection after renal transplantation or different forms of diabetes (Watts *et al.*, 1986). NAG, a high molecular mass lysosomal enzyme (MW 140,000) mainly present in the proximal convoluted tubule (Stolarek *et al.*, 1989) is an extremely sensitive index of renal parenchymal damage, a reliable tool for monitoring kidney disease and an early indicator of immune rejection in patients with renal allografts (Horak *et al.*, 1981).

Lysozyme, a low molecular weight protein (14,500) found in human peripheral plasma, is almost entirely of extrarenal origin. Within the kidneys, lysozyme is filtered in the glomerulus and then reabsorbed and degraded by proximal tubular epithelial cells. Little or no lysozyme activity is detectable in normal urine and, in the absence of leukaemia or bowel disease, lysozymuria is a sensitive marker for renal tubular damage or dysfunction (Harrison *et al.*, 1968; Hayslett *et al.*, 1968; Horpacsy *et al.*, 1978; Shima *et al.*, 1986; Urivetsky *et al.*, 1989). Except for IgG levels, NAG, albumin and lysozyme levels were slightly elevated in the patients before treatment. These statistically non-significant increases were also observed by Assimos *et al.* (1989) in NAG and galactosidase levels. They may be truly non-significant or they may suggest a persistent minor impairment of renal function due to the kidney stone.

In contrast to the findings of Wilbert *et al.* (1988), we found no significant change in the IgG level; in accordance with their findings, however, there was a significant change in the albumin level after lithotripsy. Since we have no data on the method used by Wilbert *et al.* (1988) for detecting IgG, this discrepancy may stem from different laboratory methods and a different lithotriptor. Not only did the mean albumin level increase, but 89% of patients showed the same trend (24/27). Like Jung *et al.* (1989) and Marcellan and Servio (1986), we found no impairment in tubular function as judged by the excretion of NAG and lysozyme; there was only a minor, non-significant increase in NAG levels in 46% of patients. Kongrad *et al.* (1988), while performing split urine collection on a small group of patients with renal calculi, found that the concentration of NAG and $\gamma$-glutamyltransferase remained the same in the treated kidney but the creatinine concentration decreased. This phenomenon was attributed to defective concentration. In the present study, the mean creatinine level decreased from 10.62±10.25 mmol to 9.41±6.65 mmol, but this was not significant. In contrast, Kishimoto *et al.* (1986) and Assimos *et al.* (1989) reported significant increases in the NAG to creatinine ratio in patients during the first 4 days after ESWL, or 24 h after treatment according to Trinchieri *et al.* (1988). A possible reason for our having missed this peak could be the sampling time, which did not include 4-day urine sampling. We found no decrease in creatinine clearance, as reported by Gunasekaran *et al.* (1989) in their rabbit kidney model, nor could we find any statistically significant increase in serum enzymes, as found by Haupt *et al.* (1989), especially in the Tucson group which received a high number of shockwaves.

It was concluded that, despite working with equipment that produced a high number of shockwaves, renal injury was minor, transient and reversible.

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# Do Stone Formers have Lower Urinary Fibrinolytic Activity than Controls?

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Summary—A comparison of urinary fibrinolytic activity between 31 stone formers and 50 controls failed to demonstrate any significant difference and so failed to confirm an earlier independent observation. This may be due to methodological and design differences between the 2 studies, but does suggest reservations about the significance of lowered urinary fibrinolytic activity as a risk factor for renal stone disease.

Dietary information from those taking part in the study suggests that a reduction of meat intake by stone formers might be associated with increased urinary fibrinolytic activity. This might account for the discrepancy between the 2 studies, in which case this observation could be of significance.

A recent study reported that urinary fibrinolytic activity is lower in renal stone patients than in matched controls (Charlton and Osmond, 1986). This suggested that at higher enzyme activities more degradation of urinary macromolecules occurred and this allowed a greater absorption of crystallisable material by the increased number of smaller molecules, thereby reducing the risk of crystalluria and lithiasis.

This argument was developed more fully in a recent review (Charlton, 1989). As supporting evidence, observations were cited that macromolecules in stone formers' urine are larger than in normal individuals (Drach *et al.*, 1982). Less directly, associations betwen cardiovascular disease and the formation of renal calculi were adduced (Vermooten, 1941; Dodson and Clark, 1946; Walker, 1961). The inference here is that lowered circulating fibrinolytic activity (associated with vascular and ischaemic heart disease) will also be reflected as lowered urinary fibrinolytic activity and therefore a greater risk for renal stones. Furthermore, there is evidence that circulating triglycerides and cholesterol may be raised in stone formers (Rao and Blacklock, unpublished results), while decreased plasminogen activator (fibrinolytic activity) has been observed under these circumstances (Glas-Greenwalt *et al.*, 1984).

Charlton (1989) suggested that a new approach to the treatment of recurrent stone disease would be to try to increase urinary fibrinolytic activity. Since any benefits of this would become apparent only after prolonged treatment, we felt it was crucial to re-examine the urinary fibrinolytic activity in stone formers and controls.

## Patients and Methods

Stone formers and age-matched controls from a previous study of diet and renal stones (Power *et al.*, 1984) were followed up; 81 of the original 145 men were located and agreed to take part. Mean nutrient levels and other socio-demographic data in those who were traced were not significantly different from those who were not traced. A 24-h urine sample and a random urine sample were obtained from each participant, aliquots of which were stored at −20°C for later analysis. All subjects were asked to complete a brief questionnaire (developed to cover up to 90% of major nutrient intake) (Cade and Margetts, 1988) which enquired about change in diet and physical activity since the original study. They were also asked about any illnesses during the previous 5 years. Urinary

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fibrinolytic activity was estimated by cleavage of a synthetic fluorogenic substrate specific for plasminogen activator activity (carboxybenzoyl-gly-gly-arg-7-aminomethylcoumarin) (Zimmerman *et al.*, 1978). This substrate, at 0.1 mg/ml, was incubated with a 20-fold dilution of urine at 25°C in 0.05 M Tris/HCl buffer, pH 7.4, and the change in fluorescence (extinction wavelength 378 nm, emission wavelength 460 nm) over a period of 1½ h was noted. Individual blanks taking into account non-specific fluorescence change were run for each sample. All urine samples were analysed in duplicate. No change in the measured activity of frozen samples was observed after 2 months and a slight fall to 89% of starting values was found after 2 years. Results are expressed as ng of product (7-amino-methylcourmarin) produced per minute per ml of urine. Strictly speaking, we measured the plasminogen activator-like (or urokinase-like) activity of the urine, but for consistency with the earlier report (Charlton and Osmond, 1986) we refer to it as urinary fibrinolytic activity, although it should be noted that it is not the same method.

## Results

Mean urinary fibrinolytic activities are presented in Table 1. These were higher in cases than controls; 24-h creatinine levels in both groups were lower than in the random samples. In all cases and controls combined, random urine sample fibrinolytic activities were significantly correlated with their 24-h urine values (r = 0.40, $P < 0.001$), suggesting that in terms of ranking subjects, a random sample would give similar results to those of a 24-h sample.

A substantial proportion of cases had altered their eating habits since being told they had stones compared with controls (26/31 (84%) versus 29/50 (58%)). Table 2 presents the mean fibrinolytic activities according to whether or not subjects reported a change in diet. A "positive" change implied a change in intake of meat (less), vegetables (more), milk products (less), fruit (more) and fluids (more). Fibrinolytic activities were significantly higher in cases who had made a change than in both controls and cases who had not made any dietary change.

**Table 1** Mean Levels of Urokinase and Creatinine in Cases and Controls

| | *Cases (n = 31)* | | *Controls (n = 50)* | | | |
|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Z** | *Two-tailed probability* |
| 24 h urokinase | 10.2 | 7.4 | 8.4 | 5.4 | −0.86 | 0.39 |
| 24-h creatinine | 8.1 | 4.5 | 7.6 | 4.1 | −0.43 | 0.67 |
| spot urokinase | 12.5 | 9.6 | 11.1 | 8.6 | −0.49 | 0.62 |
| spot creatinine | 11.2 | 6.0 | 13.1 | 6.5 | −1.05 | 0.29 |

*Mann-Whitney U Test.

Table 3 presents the mean urinary fibrinolytic activities in various dietary change categories. The largest difference was apparent in cases who had reduced their meat intake. Fibrinolytic activity was

**Table 2** Urokinase Activity by Dietary Change in Cases and Controls

| | *Cases* | | | *Controls* | | |
|---|---|---|---|---|---|---|
| | *No.* | *Mean* | *SD* | *No.* | *Mean* | *SD* |
| 24-h urokinase | 31 | 10.2 | 7.4 | 50 | 8.4 | 5.4 |
| No dietary change* | 5 | 7.8 | 5.7 | 21 | 9.7 | 6.0 |
| "positive" dietary change | 26 | 10.6 | 7.6† | 29 | 7.4 | 4.7 |

*Change from original survey; for vegetables, meat, milk products, fruit and fluids.
†Two-tailed *t* test: $P = 0.015$ for comparison with controls.

**Table 3** Urokinase Activity by Change of Diet in Last 5 Years

| | *Cases* | | | *Controls* | | |
|---|---|---|---|---|---|---|
| *Dietary change** | *No.* | *Mean* | *SD* | *No.* | *Mean* | *SD* |
| Meat | | | | | | |
| No change | 22 | 8.8 | 6.7 | 43 | 8.6 | 5.2 |
| Less | 8 | 14.4 | 8.5 | 6 | 5.2 | 4.4 |
| Vegetables | | | | | | |
| No change | 22 | 10.4 | 7.9 | 37 | 8.6 | 6.5 |
| More | 8 | 10.3 | 6.7 | 13 | 7.9 | 5.0 |
| Milk products | | | | | | |
| No change | 10 | 9.1 | 8.3 | 34 | 9.9 | 5.6 |
| More | 2 | 12.4 | 1.2 | 3 | 5.8 | 2.2 |
| Less | 12 | 10.6 | 7.6 | 13 | 5.1 | 3.3 |
| Fruit | | | | | | |
| No change | 18 | 10.0 | 8.5 | 32 | 8.0 | 5.9 |
| More | 11 | 11.2 | 5.8 | 16 | 9.4 | 4.7 |
| Less | 1 | 4.6 | — | 2 | 6.2 | 0.3 |
| Fluid | | | | | | |
| No change | 15 | 11.3 | 7.1 | 39 | 8.3 | 5.5 |
| More | 15 | 9.3 | 7.9 | 6 | 9.3 | 6.2 |
| Less | — | — | — | 5 | 7.9 | 4.2 |

*Questionnaire not completed sufficiently by 1 case and 1 control.

nearly doubled in those who now ate less meat than in those who had not changed. The difference was not statistically significant ($F = 1.62$; $P = 0.37$).

There was no trend in urinary fibrinolytic activity in the different age groups, nor was there any difference in mean levels between those engaged in more vigorous physical activities. Similarly, there was no difference in fibrinolytic activity between subjects in different body weight categories. Ten cases and 2 controls reported having passed a stone or having further investigation or follow-up since the original survey. Mean urinary fibrinolytic activities were not statistically different between those reporting a recent stone incident ($\bar{x} = 9.4$) and those who did not ($\bar{x} = 8.8$).

There were no significant correlations between any dietary intake variables and 24-h urinary fibrinolytic activity in cases and controls combined (for example: calcium versus fibrinolytic activity $r = 0.04$; $P = 0.7$; vitamin C $r = 0.1$; $P = 0.4$).

## Discussion

This study has not shown reduced urinary fibrinolytic activity in men with renal stones compared with age-matched controls. The results therefore do not support the recent finding by Charlton and Osmond (1986) of lower values in stone formers. Five years elapsed between subjects in the present study being diagnosed and the measurement of their urinary fibrinolytic activity. Nevertheless, during that time a number of cases manifested a continuing propensity for stone formation and therefore adverse urinary risk factors despite the passage of time. This is consistent with the natural history of idiopathic stone, which is recognised as a disease with high recurrence rates in the absence of effective management to reduce urinary risk factors.

The evidence presented in Tables 2 and 3 suggests that cases have changed their dietary style since diagnosis and accepted the advice given then; this alteration has tended to increase urinary fibrinolytic activity. It is therefore possible that had we measured this activity at the time of the original diagnosis we might have found lower levels.

An interesting finding in the present study is the apparently beneficial effect of reducing meat intake on levels of urinary fibrinolysis. We were unable to determine meat consumption, only change since the original survey.

A number of studies have looked at the dietary profile of stone formers and these have been conflicting. Robertson *et al.* (1979) and Coe *et al.* (1976) observed in unmatched studies a higher animal protein intake amogst stone formers. Robertson *et al.* (1979) further observed that the effect of protein of vegetable origin was the same between patients and a control series. However, other matched case control studies (Griffith *et al.*, 1981; Power *et al.*, 1984; Wasserstein *et al.*, 1987; Fellström *et al.*, 1989) have been unable to confirm these dietary differences, although the type of case may not have been similar in each. For instance, differences exist in various parameters of the single compared with the recurrent stone former, the latter featuring in the studies in which animal protein intake was observed to be higher. Robertson *et al.* (1979) showed that urinary risk factors for calcium oxalate stone were increased by the intake of animal protein. This and other observations led to dietary advice currently given to stone formers which basically involves the lowering of the nutrient density of the diet, particularly in respect of animal proteins and refined carbohydrates. Subsequent dietary compliance has been observed to be better than with some other diet-controlled diseases (Rao *et al.*, 1984). This study tends further to confirm this observation and thus provide a possible reason for the discrepancy between our findings and those of Charlton (1989).

The observation in this study associating higher urinary fibrinolytic activity with lower meat consumption is clearly of interest and will be pursued further. If this observation is subsequently confirmed and reduction in meat intake is observed to increase urinary fibrinolytic activity, the risk of further stone formation may be reduced if the hypothesis of Charlton (1989) is true. In addition, if urinary fibrinolysis reflects circulating fibrinolytic activity, it will also have positive implications regarding thrombogenic cardiovascular disease.

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# Renal Angiomyolipoma: Report of 24 Cases

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Summary—A series of 24 patients with renal angiomyolipoma was reviewed. Their ages ranged from 10 to 70 years (average 41). Four cases were associated with tuberous sclerosis, 1 with spinal neurilemmoma, 1 with transitional cell carcinoma and another with renal tuberculosis.

The presenting symptoms in decreasing frequencies were flank pain, mass, haematuria, fever, syncope and respiratory distress. Although it has often been said that angiomyolipomas associated with tuberous sclerosis are small and asymptomatic, all 4 such patients in this study had large symptomatic tumours. Before the advent of CT scan and ultrasonography, the pre-operative diagnostic rate for cases unassociated with tuberous sclerosis was 10% (1/10). With the combined use of these 2 modalities, the diagnostic rate increased to 60% (6/10).

Most patients in this series were treated with nephrectomy. However, equally good outcomes occurred in 2 patients who received partial nephrectomies. Pre-operative diagnosis now makes it possible to consider more conservative management.

The term angiomyolipoma (AML) of the kidney was first introduced by Morgan *et al.* in 1951 to denote an uncommon type of renal tumour with the histological components of thick-walled vessels, smooth muscle cells extending outward from the vessels in a peritheliomatous fashion and fat cells of the adult and fetal types. The tumour is also referred to as renal hamartoma, one containing tissues normally present in the organ but abnormal in their arrangement, quantity and degree of maturation.

In a histopathological study of 8501 renal tumours, Hajdu and Foote (1969) found 27 cases of AML (0.3%). Clinically, 2 distinct types of renal AML have been noted. The first is found in patients with tuberous sclerosis and 20 to 50% of renal AMLs occur in such patients; 40 to 80% of patients with tuberous sclerosis exhibit AMLs which are often multiple and bilateral (Heckl *et al.*, 1987). The second type is unassociated with tuberous sclerosis but histologically indistinguishable from the first type. Patients without tuberous sclerosis are mostly women between the ages of 35 and 60 years (Petersen, 1986) and they usually present with large, unilateral and symptomatic renal masses.

The present study comprised 24 cases of pathologically proved renal AML; 23 were seen at the National Taiwan University Hospital during the past 15 years and 1 at the National Cheng Kung University Hospital in the last 1½ years. This report summarises their clinical manifestations and emphasises the changing trend in diagnosis and treatment.

## Patients and Methods

A total of 23 cases of renal AML diagnosed between September 1974 and October 1987 were found in the pathology registry at the National Taiwan University Hospital. The patients' hospital charts, histopathology reports and imaging studies (intravenous urography, angiography, ultrasonography, computed tomography) were reviewed. A questionnaire was sent to each patient to check his/her present status. Information on demography, clinical presentation, diagnosis, treatment and follow-up was gathered and analysed.

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Another case of AML associated with tuberous sclerosis was encountered at the National Cheng Kung University Hospital in November 1988 and was included for analysis.

Seven patients were male and 17 female, all ethnic Chinese. The youngest patient was a 10-year-old girl and the oldest a 70-year-old man. The mean age was 41 years (44 in the males and 40 in the females).

### *Association with other conditions*

Four females (aged 10, 22, 27 and 28 years) showed typical manifestations of tuberous sclerosis, including a history of seizure, mental retardation, adenoma sebaceum and peri-ventricular calcifications (Fig. 1). Another patient had previously undergone excisional surgery for a T6 spinal neurilemmoma. In 2 other patients undergoing nephrectomy, 1 for transitional cell carcinoma of the renal pelvis and the other for renal tuberculosis, AML was found accidentally in the specimens.

### *Tumour size and laterality*

In 11 cases the tumours were on the right side and in 9 they were on the left. All 4 tuberous sclerosis patients had bulky bilateral and multiple tumours measuring from 1 to 30 cm in diameter (Table 1).

**Table 1** Tumour Sizes* in Tuberous Sclerosis Patients

| *Age of patients (years)* | *Tumour size right/left (cm)* |
|---|---|
| 10 | 15/6 |
| 22 | 14/24 |
| 27 | 30/12 |
| 28 | 14/7 |

*Only the size of the largest tumour is shown.

### *Clinical presentation*

The presenting symptoms are listed in Table 2. Those most frequently encountered were flank pain and mass. Two patients had hypovolaemic shock due to tumour rupture. In 1 case the tumour was found accidentally during a sonographic examination. All tuberous sclerosis patients had symptomatic tumours.

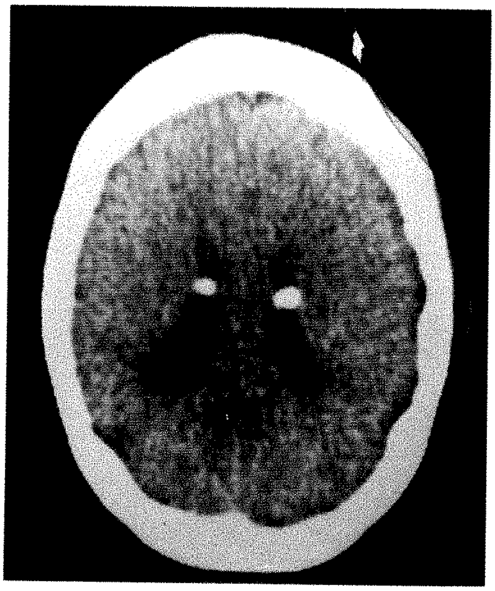

**Fig. 1** A case of bilateral AML associated with tuberous sclerosis. Brain scan at ventricular level showed peri-ventricular calcifications.

### *Diagnosis*

Of the 24 cases, 11 were encountered before the use of CT scan. Among these, 1 correct diagnosis of bilateral renal AMLs associated with tuberous sclerosis was made on clinical ground together with tumour needle biopsy. The other 10 patients all had operations. In only 1 patient with ultrasonographic evidence of a highly echogenic tumour was the correct pre-operative diagnosis suggested.

The other 13 patients were encountered after the advent of CT scanning and ultrasonography. AMLs were often detected as echogenic tumours with low CT attenuation values (Figs 2, 3, 4, 5). Among these, 3 cases associated with tuberous sclerosis were diagnosed clinically: 2 were confirmed by needle biopsies and the other surgically. The other 10 patients underwent surgery. Among them, 6 correct pre-operative diagnoses of AML were made.

## Results

Of the 20 patients without tuberous sclerosis, 16 were treated by nephrectomy. One had nephroureterectomy for concomitant transitional cell carcinoma of the kidney. Another with a huge tumour

**Table 2** Presenting Symptoms

| *Symptom* | *Number (%)* |
|---|---|
| Flank pain | 17 (70) |
| Mass | 9 (38) |
| Haematuria | 5 (21) |
| Fever | 2 (8) |
| Syncope | 2 (8) |
| Respiratory distress | 1 (4) |
| Asymptomatic | 1 (4) |

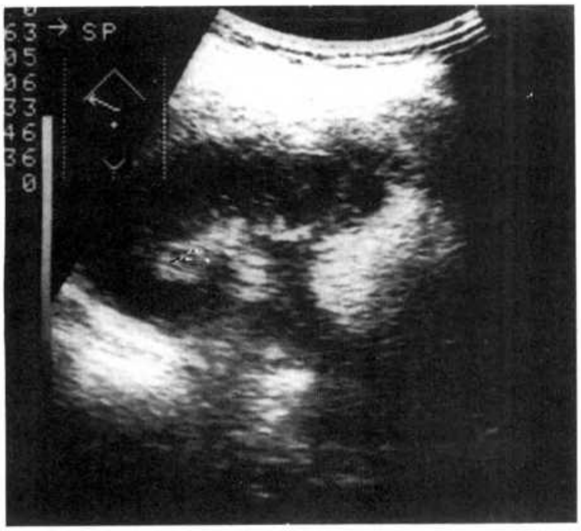

**Fig. 2** Sonography of AML. Highly echoic tumour at lower pole of the right kidney.

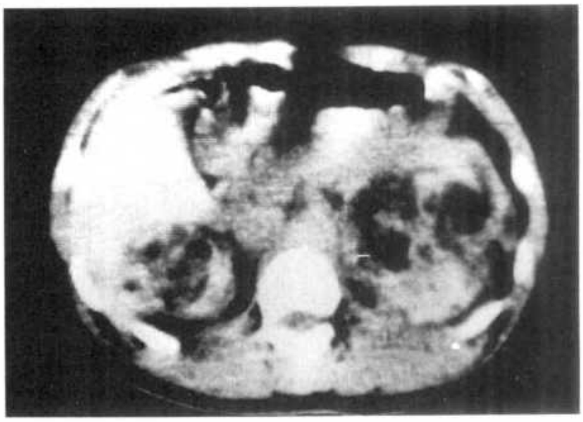

**Fig. 4** Bilateral renal AML associated with tuberous sclerosis in a 28-year-old female. Low density tumours in both kidneys.

received pre-operative embolisation followed by nephrectomy. Two patients had a pre-operative diagnosis of AML and underwent partial nephrectomy after frozen section confirmation. All except 1 of these patients are alive and well and tumour-free. The longest follow-up has been 15 years. The patient with transitional cell carcinoma died of metastasis.

Among the 4 tuberous sclerosis patients, a 10-year-old girl received unilateral nephrectomy for a large symptomatic tumour which had been considered as Wilms' tumour pre-operatively. She has been followed up for 7 years and has AML in the contralateral kidney. Another patient had huge tumours that compressed the lungs (Fig. 6). She died of respiratory failure and sepsis soon after diagnosis. The remaining 2 patients did not undergo surgery and have been followed up for 4 and 10

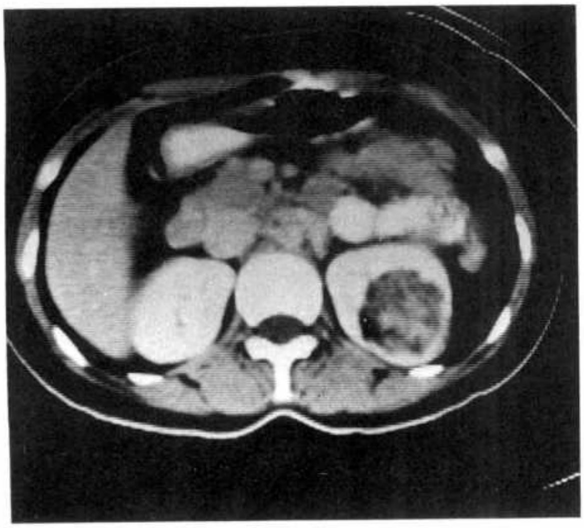

**Fig. 3** CT scan of AML. Low fat density tumour in the left kidney.

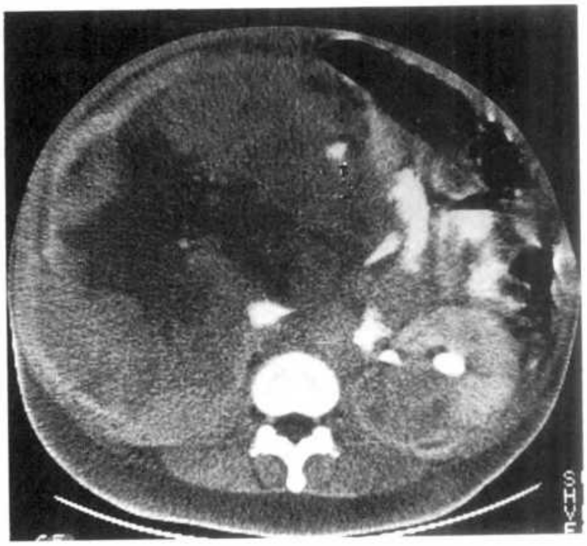

**Fig. 5** Bilateral renal AML associated with tuberous sclerosis in a 27-year-old female. Huge tumour in the right kidney and smaller tumour on the left side.

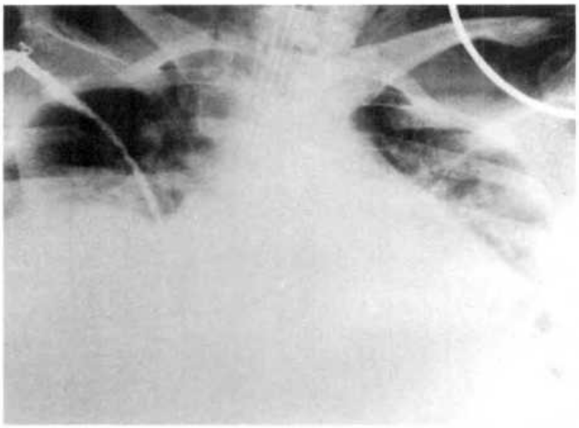

**Fig. 6** Same patient as in Figure 5. Lung compressed by the tumour.

years respectively. Both have remained symptomatic with flank pain and mass. Follow-up ultrasonographic examinations have shown slow growth of the tumours.

## Discussion

The reported frequency of association between AML and tuberous sclerosis varies from 80 to 0% (Bret *et al.*, 1985). In the present series, 16.7% (4/24) of the AML patients had tuberous sclerosis. Moreover, 1 patient had a history of spinal neurilemmoma. Whether this lesion should be considered as a stigma of tuberous sclerosis is arguable. It has often been quoted that AMLs associated with tuberous sclerosis are usually bilateral, multiple, small and asymptomatic (Wong *et al.*, 1980). However, the 4 patients presented in this study all had large symptomatic tumours. Thus AMLs associated with tuberous sclerosis are not always silent. Such patients should be evaluated regularly and treated appropriately.

Cases of AML associated with renal carcinoma have been reported (Graves and Barnes, 1986; Blute *et al.*, 1988). Waters *et al.* (1986) reported another case of simultaneous renal angiomyolipoma and oncocytoma. The coexistence of AML with renal tuberculosis and with transitional cell carcinoma presented in this series were rare occurrences too.

AMLs are generally regarded as benign. Involvement of the spleen and regional lymph nodes (Bloom *et al.*, 1982; Hulbert and Graf, 1982) has been attributed to the multicentric nature of the lesion rather than to metastatic behaviour. Vascular invasion by AMLs to the renal vein (Byrne *et al.*, 1988), inferior vena cava (Camunez *et al.*, 1987) and even the right atrium (Rothenberg *et al.*, 1986) has also been reported. Whether this represents a true malignant invasion or just a result of continual tumour growth is controversial. However, the one death in the present series shows that AML does have the potential for relentless enlargement.

Wong *et al.* (1980) advised that the diagnosis of AML should be borne in mind by all surgeons, since 25% of patients with renal AML described in the literature presented with severe abdominal pain and/or shock which necessitated emergency laparotomy. In the present series, only 2 patients underwent emergency nephrectomy for tumour rupture and shock. The leading symptoms were flank pain, flank mass and haematuria, although fever was the presenting manifestation in 2 patients. A similar case report of AML associated with fever of unknown origin was made by Vekemans *et al.* (1987).

The combined use of CT scanning and ultrasonography has become the mainstay in the clinical diagnosis of AML and has increased the accuracy of pre-operative diagnosis for cases unassociated with tuberous sclerosis in this series from 10% (1/10) to 60% (6/10). AMLs can be demonstrated as the most echogenic form of renal tumours due to their high fat content. However, this pattern is not always pathognomonic since other causes of echogenic lesions, including renal carcinoma, liposarcoma, lipoma, oncocytoma, cavernous haemangioma and renal sinus lipomatosis may also exhibit a similar picture. This diagnostic dilemma can often be solved by means of CT scanning. CT diagnosis of AML requires identification of the fat component in the tumour. This usually stands out as a lesion with low attenuation value. Lesions smaller than 2 cm may be difficult to diagnose owing to partial volume effect. On the other hand, a haemorrhage within the tumour may increase the attenuation value to above that of fat. AMLs composed of a scanty amount of mature fat or a high proportion of immature fat also have increased attenuation (Heckl *et al.*, 1987).

With pre-operative diagnosis of the tumour, the role of nephrectomy has declined. For small asymptomatic tumours, surveillance is all that is required. With symptomatic AML, renal conserving operations, including tumour excision or partial nephrectomy, are preferred if possible. However, it is important that conservation should never compromise completeness. Percutaneous transluminal embolisation is also used for treatment and control of bleeding (Eason *et al.*, 1979).

In conclusion, some angiomyolipomas can be more harmful than generally believed. All patients not receiving surgical treatment, regardless of the presence or absence of tuberous sclerosis, must be observed closely. Intervention should be considered in the event of progressive tumour growth. On the other hand, considering the essentially benign nature of AML and the improvement in preoperative diagnosis, a conservative policy is both desirable and realistic.

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# Small Cell Carcinoma of the Urinary Tract

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Summary—Small cell carcinomas of the urinary tract are rare, but lethal. We report 3 cases of primary small cell carcinoma of the kidney, urinary bladder and prostate with light microscopic, immunohistochemical and electron microscopic findings. One patient with small cell carcinoma of the prostate died of disseminated disease 2 years after diagnosis and another patient with small cell carcinoma of the urinary bladder was free of tumour after 6 months. A partial remission was induced in the third patient with distant metastases of small cell carcinoma of the kidney by using chemotherapy protocols similar to the drug regimens for small cell carcinomas of the lung; the patient survived for 5 months. Immunohistochemical studies revealed the absence of argyrophilic immunostaining of tumour cells in all 3 cases, positive staining for keratin in 2 and staining for neuron-specific enolase in all 3. In the third patient, reactivity for prostate-specific antigen was negative. Dense-core, membrane-bound granules were identified in the cytoplasm of 2 patients. The paraneoplastic syndrome was not found, indicating that in considering the occurrence of ectopic hormones, specific cytoplasmic granules of origin need not be implicated. Recognition of this distinct entity requires full consideration of morphological, immunohistological, ultrastructural and biological features. In order to define the origin of this tumour more clearly and to evaluate the effectiveness of chemotherapy, larger series of patients are needed.

Extrapulmonary small (oat, undifferentiated) cell carcinomas have been reported increasingly in recent years. Primary sites include the parotid gland (Kramer *et al.*, 1983), oesophagus (Briggs and Ibrahim, 1983), stomach (Eimoto *et al.*, 1980), pancreas (Reyes and Wang, 1981), gallbladder (Albores-Saavedra *et al.*, 1984), colon (Mills *et al.*, 1983), uterine cervix (Albores-Saavedra *et al.*, 1976), endometrium (Olson *et al.*, 1982), skin (Taxy *et al.*, 1980; Silva *et al.*, 1984) and other more unusual sites (Richardson and Weiland, 1982). In 1984, Capella *et al.* reported the first case of primary small cell carcinoma in the kidney. In 1978, Aoyama reported the first case of this tumour in the urinary bladder and Jarett *et al.* (1964) reported the first case in the prostate, with production of an ACTH-like substance. Although no firm conclusions regarding histogenesis and effective chemotherapy for small cell carcinomas can be drawn, owing to the small number of patients, we present 3 patients with these tumours in the kidney, urinary bladder and prostate. We also review previously reported cases.

## Case Reports

*Case 1.* A 37-year-old male complained of back pain with tinnitus of the left ear for 3 months, complicated by headache and deviation of tongue to the left for a few days before admission. CT scan of the brain and a bone scintigraphic scan revealed multiple metastatic lesions. An intravenous urogram and CT scan of the abdomen showed a lesion in the left kidney. A left nephrectomy was performed. A 4×4×3.5-cm white, solid tumour occupied the middle pole of the left kidney. No tumour extension into the inferior vena cava, posterior peritoneum or posterior abdominal wall was found. A full investigation, including pulmonary CT scan, was done and no tumour was found in other possible primary sites. Chemotherapy that included Endoxana, epirubicin, VP-16 and Oncovin was begun and partial remission was induced after 2 courses.

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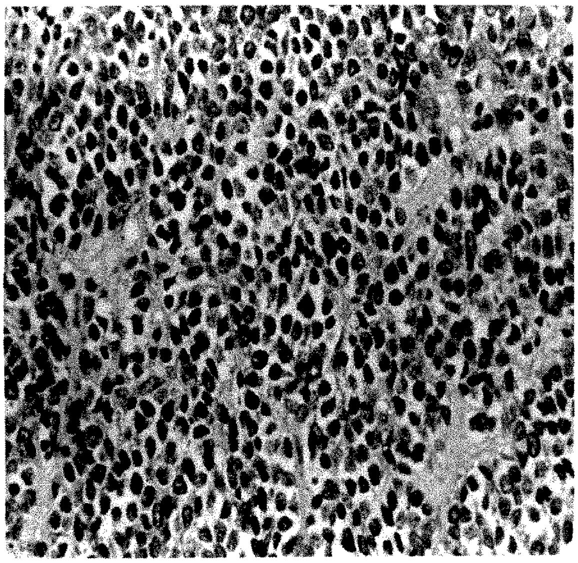

**Fig.** Small cell carcinoma of the kidney shows small, oval to spindle tumour cells with hyperchromatic nucleus, inconspicuous nucleolus and scanty cytoplasm (H and E × 200).

Sections of the tumour showed a diffusely infiltrating anaplastic carcinoma comprising cells with scanty cytoplasm and small, markedly hyperchromatic nuclei (Fig.). There was microscopic evidence of capsular and vascular invasion. The tumour showed positive immunostaining for keratin and neuron-specific enolase but not for argyrophilic (Grimelius) or argentaffic (Fontana-Masson) silver impregnation stain.

The tumour was examined by means of electron microscopy and demonstrated scanty cytoplasm that contained membrane-bound, dense-core granules measuring 100–200 nm in diameter.

*Case 2.* A 74-year-old male was admitted with gross haematuria and dysuria of 1 month's duration. Intravenous urography showed a filling defect in the urinary bladder with non-visualisation of the left ureter. Cystoscopy revealed a 5-cm polypoid tumour arising from the left posterolateral wall of the urinary bladder. The tumour was resected and reported as an undifferentiated carcinoma of the bladder with invasion into the muscular wall. Extensive investigations showed no evidence of distant metastases. A radical cystectomy was performed but involvement of regional lymph nodes was shown on microscopic examination. The patient did well for 6 months without further treatment. Histological examination of the tumour revealed a deeply invasive epithelial neoplasm composed of clusters of small cells with hyperchromatic nuclei resembling pulmonary oat cell carcinoma. The results of the immunostain were identical to those of Case 1. Intracytoplasmic membrane-bound, dense-core granules were also observed under electron microscopic examination.

*Case 3.* A 67-year-old male presented with urinary obstruction. Transurethral prostectomy revealed moderately differentiated adenocarcinoma. He was treated with oral oestrogens and underwent orchiectomy. He remained clinically well for a further 20 months, when he was found to have extensive metastatic involvement of the retroperitoneal lymph nodes, lumbar vertebral bodies and pelvis. No pulmonary neoplasm was found on chest X-ray. The patient had received nephrostomy tube drainage of the right kidney due to obstructive uropathy. He refused further therapy and presented 5 weeks later with a malignant pleural effusion. Ultrasonically guided aspiration biopsy of the abdominal mass was performed and revealed sheets of undifferentiated small cell carcinoma of the oat cell type. The tumour cells were negative for prostate specific antigen, keratin, argyrophilic or argentaffic stain but positive for neuron-specific enolase. The tumour cells of the biopsy specimen were relatively poorly preserved for electron microscopic examination. Chemotherapy with doxorubicin was started but he died shortly therafter without evidence of response.

## Discussion

Identification of small cell carcinomas arising in non-pulmonary sites has increased in recent years, probably reflecting the increasing use of the electron microscope and immunohistochemical study in diagnostic pathology. Recognition of small cell carcinoma of the urinary tract as a biological, morphological and immunohistochemical correlate of small cell carcinoma of the lung not only has therapeutic implications but also contributes to the further understanding of the biological derivation of such tumours.

The true incidence of this neoplasm in the urinary tract is unknown because few cases are reported. Tetu *et al.* (1987b) reviewed 215 stage C adenocarcinomas of the prostate in 20 years and found this tumour to have an incidence of only 1%. The clinical features, biological behaviour, immunological markers and electron microscopic findings in small cell carcinoma of the prostate and urinary bladder are better understood because of the large number of cases reported by Tetu *et al.* (1987b) and Ro *et al.* (1987), together with a review by Swanson *et al.* (1988). Metastatic carcinoma of the lung to the prostate must be considered in the differential diagnosis of primary carcinoma of the prostate, although the incidence is very low. Distant metastases were a common finding when the patient developed small cell carcinoma.

All 3 tumours in this study fulfilled the morphological criteria for small cell carcinoma as established for lung tumours by the World Health Organization. Small cell carcinoma was composed of uniform small malignant cells measuring up to twice the diameter of normal lymphocytes and possessing a pyknotic round to oval nucleus, evenly distributed chromatin, inconspicuous nucleoli and scanty cytoplasm.

We reviewed the literature on small cell carcinoma of the prostate and Table 1 shows the clinical data, immunohistochemical and electron microscopic findings. The age of the patients ranged from 30 to 89 years (median 67). An initial diagnosis of adenocarcinoma of the prostate was reported in 14 of 33 cases (42%). Distinct areas of transition between the adenocarcinoma and small cell carcinoma were apparent in many cases. According to the literature, 24 of 33 patients died of their disease with a median overall survival of 14 months from the initial diagnosis of prostatic malignancy. Of those who died, 11 presented initially with an adenocarcinoma and lived for periods ranging from 8 days to 9 years (median 25 months). Of the patients presenting with small cell carcinoma of the prostate, 13 died within 1.5 years (median 5.2 months). Distant metastases were found in all cases. The most frequent metastatic sites were the pelvic lymph nodes and bone. The features of our patient, together with those previously reported, show that these tumours behave more aggressively than the usual prostatic carcinomas, but have similar features and metastatic spread. Endocrinological manifestations such as Cushing's syndrome were observed in 4 of 33 cases (12%). The low incidence may be related to the specific neuroendocrine differentiation of the heterogeneous tumour cells.

Wenk *et al.* (1977) suggested that prostatic small cell carcinoma is biologically and histogenetically different from prostatic carcinoma in its common form and the former derives from argentaffin or argyrophile cells normally present in the prostatic epithelium, so-called APUD (amine precursor uptake and decarboxylation)-neural crest cells (Pearse, 1969) with characteristically neuroendocrinal, immunohistochemical and electron microscopic features. Vuitch and Mendelsohn (1981), Schron *et al.* (1984), Ghandur-Mnaymneh *et al.* (1986), Tetu *et al.* (1989) and Sarma and Weilbaecher (1989) found that some of the prostatic small cell carcinomas arose in association with and during the course of progression of regular prostatic carcinoma. They suggested that small cell carcinoma of the prostate might be part of a spectrum of divergent differentiation of the stem epithelial cells with totipotential capabilities.

Neuron-specific enolase (NSE) is a useful marker for endocrine tumours, but NSE and intracytoplasmic dense-core secretory granules were not found in all cases of small cell carcinoma of the prostate. This accords with small cell carcinoma of the urinary bladder (Table 2) and the kidney (Table 3). It indicates that not all small cell carcinomas are necessarily of a neuroendocrine nature. Schron *et al.* (1984) reported that loss of prostate specific antigen in small cell carcinomas of the prostate may have clinical and biological implications. In their study, 3 of 26 cases (11%) still possessed prostate specific antigen in the tumour cells.

The paraneoplastic syndromes with inappropriate secretion of hormones such as ACTH (Jarett *et al.*, 1964; Wenk *et al.*, 1977; Vuitch and Mendelsohn, 1981), antidiuretic hormone (Ghandur-Mnaymneh *et al.*, 1986) and the associated myasthenic syndrome have been reported but are rare.

A review of the literature on small cell carcinoma of the urinary bladder (Aoyama, 1978; Aozasa *et al.*, 1979; Anichkov *et al.*, 1979; Colby, 1980; Cramer *et al.*, 1981; Davis *et al.*, 1983; Kim *et al.*, 1984; Ibrahim *et al.*, 1984; Reyes and Soneru, 1985; Partenen and Aisikainen, 1985; Ordonez *et al.*, 1986; Mills *et al.*, 1987; Swanson *et al.*, 1988; Podesta and True, 1989; Blomjous *et al.*, 1989), including the present series, shows that 55 cases have been well documented. The clinical course and biological behaviour of these tumours resembled those of small cell carcinomas of the prostate (Tables 1 and 2). The sex ratio of male to female was 45:10 and ages ranged from 30 to 82 years (median 67); 32 of 55 patients died of their disease over periods ranging from a few days to 12 months after diagnosis (median 6.8 months). High percentages of NSE positivity (34/38) and intracytoplasmic dense-core granules (36/50) were noted (Table 2). Most authors agreed that these lesions originated from undifferentiated stem cells present in the basal cell layer of the transitional epithelium (Kim *et al.*, 1984).

In this study, we reported a young man whose small cell carcinoma of the kidney was smaller than those previously reported (Capella *et al.*, 1984; Tetu *et al.*, 1987a). As shown in Table 3, the tumours occurred mainly in female patients and on the left side. Small cell carcinomas of the kidney also tended to metastasise rapidly and the prognosis was poor. Most patients had neuroendocrine immunohistochemical and electron microscopic features.

No definite data are available to indicate the best treatment for small cell carcinoma of the urinary tract because of the aggressive and often far

Table 1 Clinical, Electron Microscopic and Immunohistochemical Findings in Small Cell Carcinoma of the Prostate

| *Author* | *Year* | *No. of cases* | *Mean age (years)* | *Initial diagnosis* | *Survival after diagnosis (mean)* | *Metastasis* | *Cushing's syndrome* | *EM* | *Argenotaffin* | *Argyrophil* | *NSE* | *Keratin* | *PSA* | *CEA* | *ACTH* | *ADH* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jarett | 1964 | 1 | 57 | SCC | 8 days | Yes | Yes | ND | ND | ND | ND | ND | ND | ND | + | ND |
| Wenk | 1977 | 1 | 62 | SCC | 22 days | Yes | Yes | + | ND | ND | ND | ND | ND | ND | + | ND |
| Vuitch | 1981 | 1 | 70 | Mixed | 25 months | Yes | Yes | + | ND | + | ND | ND | ND | ND | + | ND |
| Schron | 1984 | 3 | 72 | AdenoCa | 16 months | 3/3 | 1/3 | 1/1 | 0/2 | 0/2 | ND | ND | 0/3 | 0/3 | 1/3 | ND |
| Hindson | 1985 | 1 | 61 | SCC | 8 months | Yes | No | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Ghandur-Mnaymneh | 1986 | 1 | 73 | Mixed | 3 months | Yes | No | ± | – | + | + | ND | – | + | + | ND |
| Tetu | 1987 | 20 | 67 | AdenoCa (9) | 2 years | 20/20 | 0/20 | 2/7 | 1/18 | 4/18 | 10/18 | ND | 3/18 | 5/18 | 0/18 | 0/18 |
| Tetu | 1987 | | | SCC (6)<br>Mixed (5) | 5 months | | | | | | | | | | | |
| Manson | 1989 | 1 | 67 | SCC | 5 weeks | Yes | No | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Sarma | 1989 | 2 | 68 | SCC | 2 months | Yes | 0/2 | 0/1 | ND | ND | ND | ND | 0/2 | ND | ND | ND |
| Tetu | 1989 | 1 | 58 | AdenoCa | 5¼ years | ? | No | ND | ND | ND | + | ND | – | ND | – | ND |
| Current study | 1989 | 1 | 67 | AdenoCa | 22 months | Yes | No | ND | – | – | + | – | – | ND | ND | ND |

EM: electron microscopy; NSE: neuron-specific enolase; PSA: prostate specific antigen; CEA: carcinoembryonic antigen; ADH: antidiuretic hormone; SCC: small cell carcinoma; AdenoCa: adenocarcinoma; Mixed: admixture of SCC and adenocarcinoma; ND: not done.

**Table 2** Clinical, Electron Microscopic and Immunohistochemical Findings in Small Cell Carcinoma of the Urinary Bladder

| *Author* | *Year* | *No. of cases* | *Mean age (years)/Sex* | *Survival after diagnosis (mean)* | *Metastasis* | *EM* | *Argyrophil* | *NSE* |
|---|---|---|---|---|---|---|---|---|
| Aoyama | 1978 | 1 | 59/M | died 12 months | + | + | + | ND |
| Aozasa | 1979 | 1 | 55/M | NET 20 months | − | + | + | ND |
| Anichkov | 1979 | 1 | 42/M | NET 12 months | − | + | + | ND |
| Colby | 1980 | 1 | 30/M | NET 12 months | − | + | − | ND |
| Cramer | 1981 | 1 | 69/M | NET 14 months | − | + | − | ND |
| Davis | 1983 | 3 | 66/M | 1 died 11 months; 2 NET 23, 28 months | 1/3 | 3/3 | 0/3 | ND |
| Kim | 1984 | 2 | 80/M | 2 died 2 months | 1/2 | 0/2 | ND | ND |
| Ibrahim | 1984 | 1 | 75/M | died 5 months | + | + | − | ND |
| Reyes | 1985 | 3 | 57/M | 2 died 6 months and days, 1 NET 36 months | 2/3 | 3/3 | ND | ND |
| Partanen | 1985 | 1 | 55/F | died 3 months | + | + | ND | ND |
| Ordonez | 1986 | 3 | 65/M | 1 died 7 months; 2 NET 12 and 2 months | 2/3 | 3/3 | ND | 3/3 |
| Mills | 1987 | 12 | 76/M10, F2 | 5 died 4 months | 8/8 | 7/7 | ND | 11/12 |
| Swanson | 1988 | 1 | 57/F | died 7 months | + | + | − | ND |
| Podesta | 1989 | 5 | 77/M4, F1 | 3 died 4 months; 2 NET 46 months | 3/5 | 3/5 | ND | 4/4 |
| Blomjous | 1989 | 18 | 68/M13, F5 | 14 died 9.4 months | 16/18 | 8/18 | 1/18 | 15/18 |
| Current study | 1989 | 1 | 74/M | NET 6 months | − | + | − | + |

EM: electron microscopy; NSE: neuron-specific enolase; NET: no evidence of tumour; ND: not done.

**Table 3** Clinical, Electron Microscopic and Immunohistochemical Findings in Small Cell Carcinoma of the Kidney

| *Author* | *Year* | *Age/Sex (years)* | *Dead after diagnosis* | *Chemo-therapy* | *Site of lesion* | *Tumour size (cm)* | *Metastasis* | *EM* | *Argeno-taffin* | *Argyro-phil* | *NSE* | *Keratin* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capella | 1984 | 68/F | Days | ND | Lt | 12 × 10 × 9 | LNs | + | ND | + | ND | ND |
| Tetu | 1987 | 56/F | 8 months | Yes | Lt | 10.5 × 9 × 9 | LNs | ND | − | − | − | + |
| | | 64/F | Alive 18 months | ND | Lt | 14.5 × 6.5 × 6 | No | + | − | + | + | − |
| | | 83/F | 1 year | Yes | Rt | 18.5 × 10.5 × 9.5 | Renal vein | − | − | − | − | + |
| Current study | 1989 | 37/M | Alive 5 months | Yes | Lt | 5 × 5 × 4.5 | Brain, bone | + | − | − | + | + |

EM: electron microscopy; NSE: neuron-specific enolase; ND: not done; LNs: lymph nodes.

advanced state of the disease at diagnosis. Hindson *et al.* (1985) reported a patient with small cell carcinoma of the prostate with transient complete remission after chemotherapy and suggested prophylactic irradiation of the brain as standard treatment for small cell carcinoma of the lung. Chemotherapeutic regimens include cyclophosphamide, doxorubicin and vincristine, which are similar to the protocols for small cell carcinoma of the lung. Although not statistically conclusive, combination chemotherapy is a promising approach in the treatment of metastatic lesions of extrapulmonary small cell carcinoma.

Small cell carcinoma of the urinary tract is a heterogeneous group of tumours whose biological behaviour, clinical course and presentation are similar to those of small cell carcinoma of the lung. The disease follows an aggressive course and has a poor prognosis. Early recognition of this distinct entity and understanding of its nature have important clinical implications regarding treatment.

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# The Effect of Verapamil on the Anti-tumour Action of Mitozantrone and Doxorubicin against Renal Carcinoma Cells *in vitro*

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Summary—Ten renal carcinomas were established in culture and their sensitivity to mitozantrone ± verapamil, as measured by (75 Se) selenomethionine incorporation, was studied. The 5 tumours with spread beyond the kidney were those in which sensitivity to mitozantrone was enhanced by verapamil. With 4 of the 10 tumours and 1 further carcinoma, similar experiments were performed using doxorubicin. This drug was more active, its anti-tumour action being related to concentration. Verapamil was more effective in potentiation of doxorubicin and this action increased in proportion to the concentration of verapamil added.

Lai *et al.* (1989), using (75 Se) selenomethionine uptake to measure protein synthesis, found that the growth of renal carcinoma cells, *in vitro*, could be inhibited by mitozantrone and doxorubicin. In general, however, renal carcinomas are not responsive to anti-cancer drugs and this may be associated with expression of the multi-drug resistance gene, MRDI, by these tumours (Kanamaru *et al.*, 1989). This gene codes for a 170 KD transmembrane glyco-protein (P 170) (Gerlach *et al.*, 1986; Gros *et al.*, 1988) which, by its action as an efflux pump, enables cells to eliminate drugs at an increased rate.

Verapamil (VPM), a calcium channel blocking agent, acts to reverse multi-drug resistance, possibly by limiting the ability of P 170 to potentiate the exocystosis of vesicles containing drugs (Willingham *et al.*, 1986; Keizer and Joenge, 1989). Mickisch *et al.* (1989) studied the effect of VPM and its (+)-enantiomer (R-VPM) on the *in vitro* anti-tumour action of vinblastine. They used cells derived from 25 primary renal carcinomas resistant to vinblastine. Both VPM and R-VPM produced a 50 to 100% decrease in viable tumour cells, using a microculture tetrazolium assay. Therefore it was of interest to investigate any action of VPM in potentiating protein synthesis inhibition by mitozantrone or doxorubicin when these drugs were added to newly established cultures of renal carcinoma cells from primary tumours.

## Patients and Methods

Eleven patients were studied. The size and stage of their tumours is shown in Figures 1 to 3. No patient had received any anti-tumour therapy prior to nephrectomy, except in the case of tumour K38, which was embolised via the renal artery immediately prior to resection. The method of preparing tumour cell suspensions, by centrifugation of the cells following enzymatic disaggregation of the solid tumour on a nycodenz column, has been described by Ferro *et al.* (1988) and Lai *et al.* (1989). The (75 Se) selenomethionine uptake assay, to measure protein synthesis, was performed according to Ferro *et al.* (1988).

### *Exposure to drugs*

Aliquots of $10^4$, $2 \times 10^4$ or $10^5$ tumour cells, obtained either directly from the nephrectomy specimen or from a derived cell culture, were cultured in medium alone or with mitozantrone (Lederle) at a concentration of 0.1, 1.0 or 5.0 μg/ml or with doxorubicin (Farmitalia) at 0.1, 0.5, 1.0 or 5.0 μg/ml for 24 h. In parallel, to separate aliquots of cells, mitozantrone

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or doxorubicin together with verapamil (Cordilox, Abbott Laboratories) at a concentration of 1.0 or 3.3 µM was added. After 24 h the tubes were centrifuged at 200 g for 5 min. The cell pellets were re-suspended in 1 ml methionine-free MEM (Gibco) and then cultured with 0.25 µCi/ml (75 Se) selenomethionine (SC12, Amersham Int.) for 48 h to measure protein synthesis. The effect of each concentration of drug(s) on protein synthesis by cell cultures was measured in triplicate.

Renal carcinoma cells, obtained from the nephrectomy specimen, prior to drug exposure and during drug exposure, were cultured in RPMI 1640 (Gibco) with 10% v/v newborn calf serum, 1% w/v glutamine and penicillin 100 u/ml, streptomycin 0.1 mg/ml and amphotericin B 0.25 µg/ml added.

### *Statistics*

For a given carcinoma the values for (75 Se) selenomethionine incorporation were subjected to a 1-way analysis of variance. The significance of any reduction in counts following exposure to a given concentration of a particular cytotoxic drug + verapamil was determined in comparison to that for cells exposed to the drug alone.

Inhibition of protein synthesis is expressed as a percentage inhibition, calculated using the formula:

$$100 \times \left[ 1 - \frac{\text{Mean counts per second (CPS) for tumour cells exposed to drug(s)}}{\text{Mean CPS for tumour cells cultured without drug}} \right]$$

A high and therefore significant variance ratio indicates the predominant source of variation as the difference in counts following different treatments rather than variation in triplicate counts for the same treatment. Variance ratios for the total data in each sample are given as a footnote to Figures 1 to 3. In Figures 1 and 2 there was correlation between a significant ratio and a significant effect of verapamil in potentiating the action of mitozantrone in 5 of 6 cases. A non-significant ratio was associated with no effect of verapamil in 3 of 4 experiments. Verapamil produced a significant increase in the action of doxorubicin in all cases except tumour K37d4 (Fig. 3). This correlated with a highly significant ratio in all experiments.

## Results

The percentage inhibition of protein synthesis following exposure to increasing concentration of mitozantrone alone or in the presence of verapamil for 10 renal carcinomas is shown in Figures 1 and 2.

Tumours K27, 28, 33, 37 and 38 were at Stage II (confined to the kidney). These tumours showed minimal or no inhibition when exposed to mitozantrone alone and, with the exception of K37, this was not related to drug concentration. The addition of verapamil produced a small increase in inhibition ($P < 0.05$) when compared with that for 1 µg/ml mitozantrone alone in 3 of the 5 tumours. Tumours K29, 32, 34, 36 and 39 were at Stage III (spread beyond the kidney) and there was significant potentiation of inhibition in the presence of verapamil in 4 of these tumours. The higher concentration (3.3 µM) of verapamil was more effective in tumours K32, K34 and K36. The levels of significance for verapamil potentiation were in general higher for the Stage III tumours.

The levels of inhibition produced by doxorubicin with or without the addition of verapamil in 5 renal carcinomas are shown in Figure 3. Doxorubicin alone produced a concentration-dependent inhibition of protein synthesis in the 5 tumours. The levels of inhibition were higher than those for mitrozantrone alone. In all 5 tumours, the addition of verapamil led to a significant increase in the level of inhibition, a concentration of 3.3 µM being more effective than 1.0 µM.

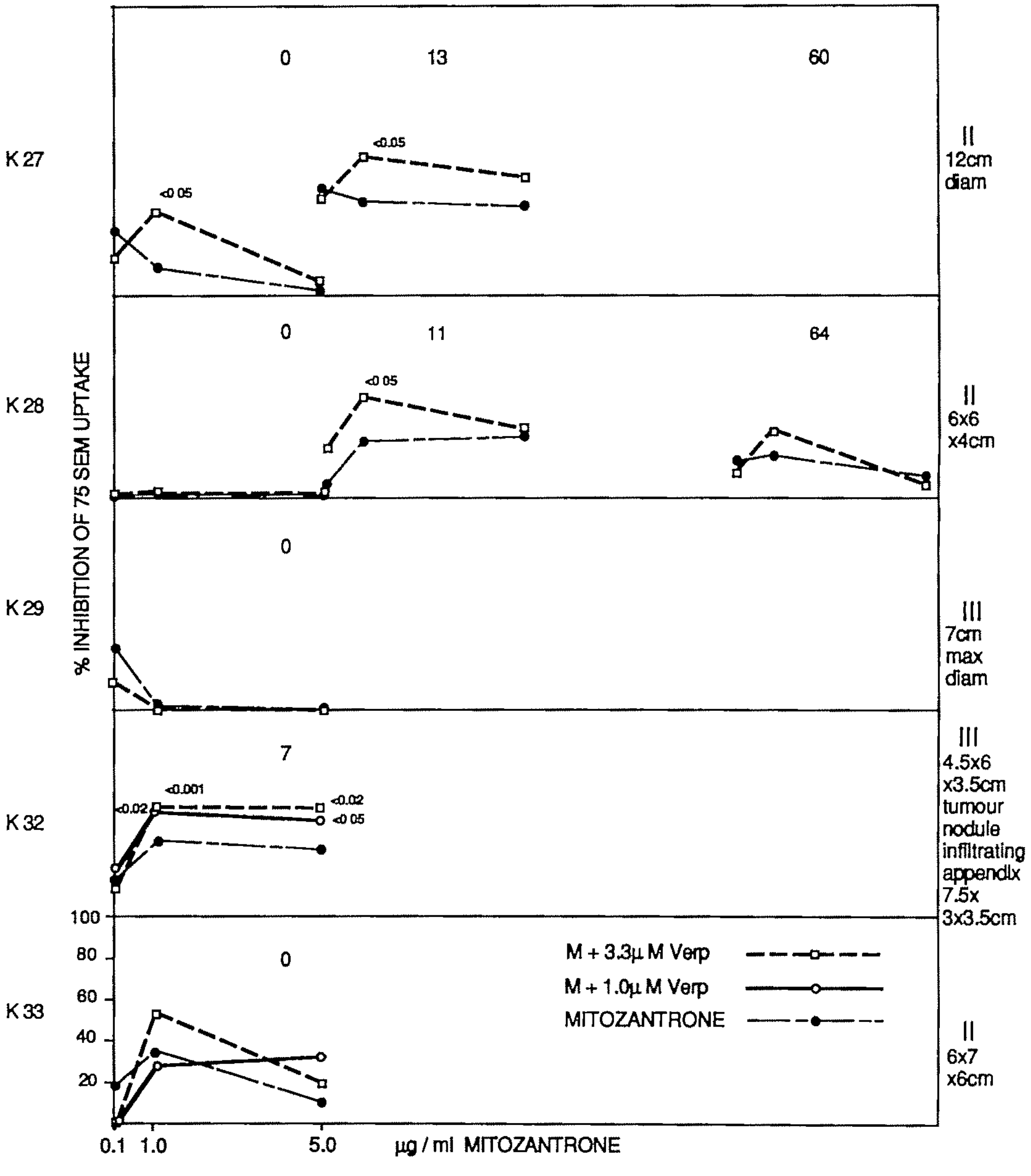
The effect of 5.0 µg/ml doxorubicin ± verapamil was also studied (data not shown). Except for the 41-day culture of K39, >90% inhibition was consistently produced by doxorubicin alone. Thus potentiation by verapamil was not possible. For K39 on day 41, inhibition with doxorubicin was 11.9% and in the presence of verapamil 1.0 µM, 38.9% ($P < 0.001$) and 3.3 µM, 68.8% ($P < 0.001$).

Repeat experiments were performed with tumour K34 using both mitozantrone (Fig. 2) and doxorubicin (Fig. 3) to study the impact of increasing the period of culture following the removal of the primary tumour. For both drugs, tumour inhibition was decreased following prolonged culture. This was also true for doxorubicin in the case of tumours K37, 38 and 39 (Fig. 3) but not for mitozantrone with tumours K27 and 28 (Fig. 1).

Verapamil alone, at either 1.0 µM or 3.3 µM concentration, produced no significant inhibition of protein synthesis by tumour cells in any experiment (data not shown).

## Discussion

The lack of concentration-dependent inhibition of protein synthesis by tumour cells exposed to

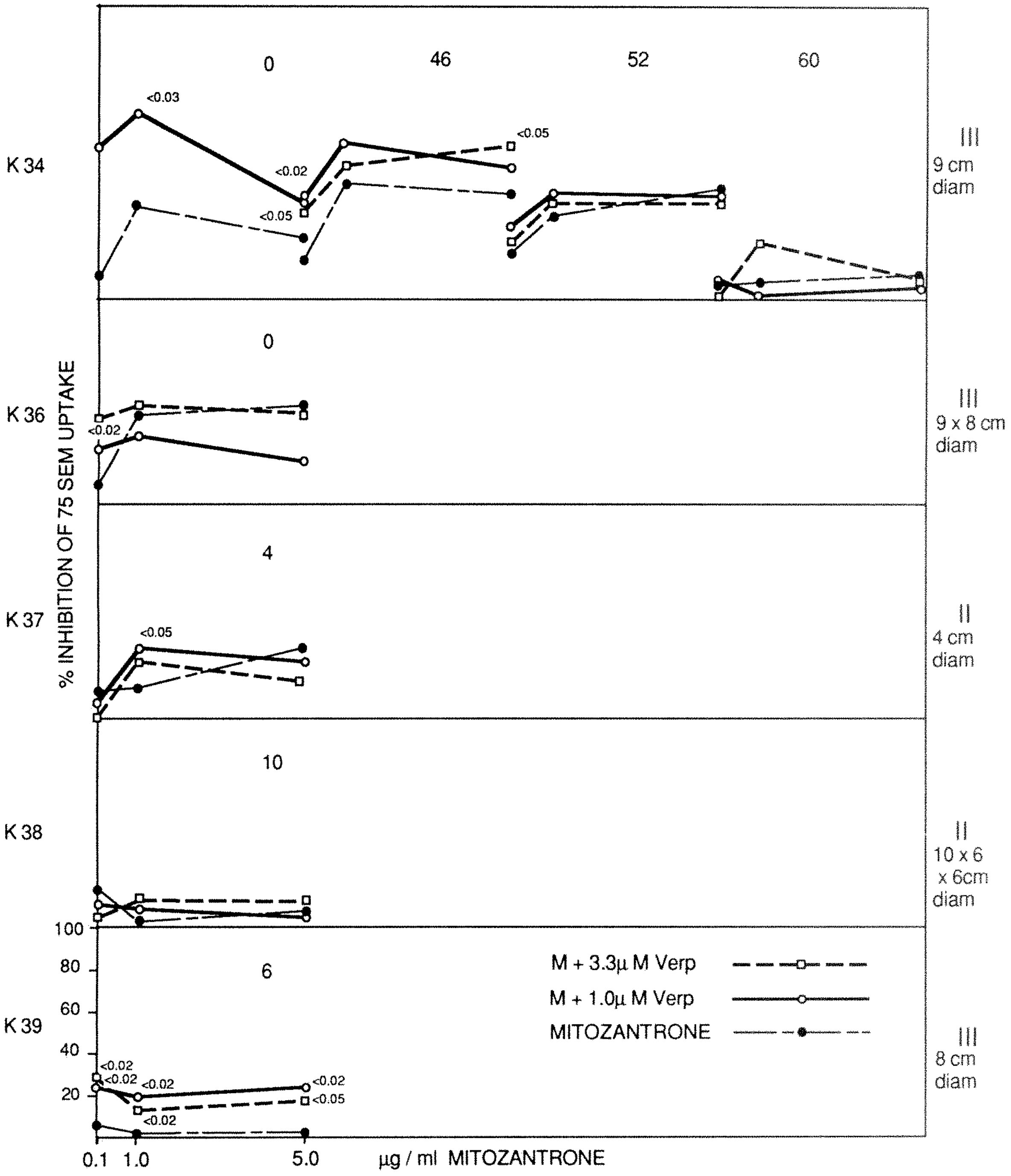


Variance Ratios F K27 2.34 <0.1 >0.05 | 9.59 <0.001

K28 0.58 >0.25 | 5.55 <0.005 >0.001 | 1.89 <0.25 >0.1

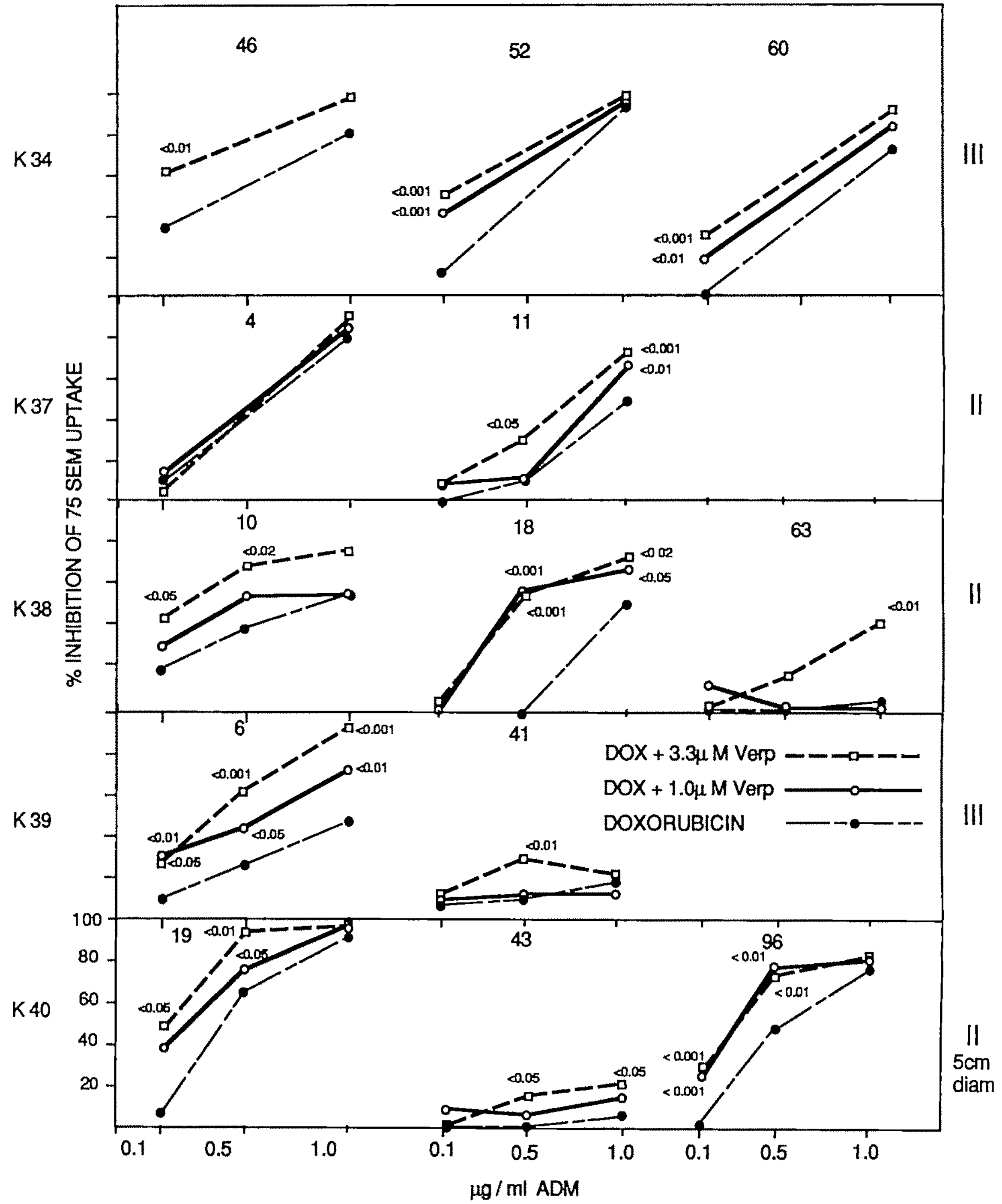
K29 1.67 <0.25 >0.1 |
K32 513.8 <0.001
K33 2.83 <0.025 >0.01

**Fig. 1** Effect of mitozantrone with or without addition of racemic verapamil on ($^{75}$Se) selenomethionine uptake by renal carcinoma cells. Cells were cultured with drug for 24 h and then with isotope for 48 h. Each point represents the mean of 3 determinations for drug exposed cells, expressed as the percentage inhibition of isotope uptake relative to the mean of 4 determinations for cells cultured in medium alone. The significance levels refer to the difference between mitozantrone + verapamil and mitozantrone alone in each case. Variance ratio (F) values indicate the degree of consistency of the data. The figure above each set of graphs is the time, in days, for which the tumour cells were cultured prior to testing for drug sensitivity. The tumour number is indicated in the left hand margin and the stage and size on the right.



Variance Ratios K34 10.9 <0.001 | 13.2 <0.001 | 16.3 <0.001 | 10.1 <0.001
K36 2.88 <0.025 >0.01
K37 201.0 <0.001
K38 11.1 <0.001
K39 31.6 <0.001

**Fig. 2** Effect of mitozantrone ± verapamil on protein synthesis by renal cell carcinomas.



Variance Ratios K34 13.2 <0.001 16.3 <0.001 10.1 <0.001
K37 201.0 <0.001 46.7 < 0.001
K38 11.1 <0.001 11.3 <0.001
K39 31.6 <0.001 11.7 <0.001
K40 71.1 <0.001 25.4 <0.001 52.9 <0.001

**Fig. 3** Effect of doxorubicin ± verapamil on protein synthesis by renal carcinoma cells.

mitozantrone alone is due to the relative insensitivity (compared with doxorubicin) of the tumours to this drug. In the present study, where tumours confined to the kidney predominated, doxorubicin was more effective than mitozantrone in inhibiting protein synthesis by renal carcinoma cells *in vitro*. In contrast, Lai *et al.* (1989) found equal sensitivity of renal carcinoma cells to mitozantrone and doxorubicin, but 17 of 23 tumours studied had spread beyond the kidney. Furthermore, sensitivity to both drugs was associated with a mixed cell pattern and/or moderate or poor differentiation.

Kanamaru *et al.* (1989) found greater amplification of the MRDI-RNA level in well differentiated renal carcinomas. Furthermore, quinidine enhanced sensitivity to doxorubicin *in vitro* (as measured by inhibition of ($^3$H) thymidine incorporation) only in cells from tumours with high MDRI-RNA expression. These findings would suggest a greater effect of verapamil in potentiating the action of drug on tumours at an early stage. However, in the present experiments, mitozantrone in combination with verapamil was more effective in inhibiting Stage III than Stage II lesions.

In parallel with its greater inhibitory action, doxorubicin showed greater potentiation by verapamil. Inhibition was directly related to the concentration of both drugs and at the lowest drug concentrations inhibition was greatest for Stage III tumours. Verapamil competitively inhibits the action of P170 in enhancing drug efflux by binding to the membrane vesicles of multidrug resistant cells (Cornwell *et al.*, 1987). Thus the level of P170 expression will determine the ability of a given concentration of verapamil to reverse drug resistance. It would therefore be expected that carcinoma cells from more advanced renal tumours with less P170 would be most susceptible to the additive effects of a cytotoxic drug and verapamil. The present findings are in accord with this prediction. The decreasing inhibition with increasing culture periods suggests the development of spontaneous drug resistance.

Occasional remissions in metastatic renal carcinoma have been recorded following treatment with doxorubicin and the present findings suggest that response could be improved by giving doxorubicin in combination with low concentrations of verapamil.

## Acknowledgement

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# Treatment of Renal Colic by Prostaglandin Synthetase Inhibitors and Avafortan (Analgesic Antispasmodic)

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Summary—In a study of the pain-relieving effect of 3 drugs commonly used to treat acute renal colic in this hospital, intravenous indomethacin and intramuscular diclofenac (prostaglandin synthetase inhibitors) were compared with intravenous Avafortan (analgesic antispasmodic). As first-line analgesics, prostaglandin synthetase inhibitors, if given intravenously, offer an effective alternative to Avafortan. Of 145 patients studied, 32 required a second injection for complete relief of pain. Administering a second dose of prostaglandin synthetase inhibitors resulted in equally significant pain relief rate even though the route was intramuscular.

The pain in acute renal colic is believed to result from increased pelviureteric pressure and distension of the renal capsule (Risholm, 1954). This increase in renal pelvic pressure stimulates the synthesis of prostaglandin in the papillary region of the renal medulla (Nishikawa *et al.*, 1977). One of these prostaglandins, $PGE_2$, has diuretic properties (Flannigan *et al.*, 1983). Thus an increase in prostaglandin synthesis results in increased diuresis and increased intensity of renal colic.

Non-steroidal analgesic anti-inflammatory drugs have been used to treat acute renal colic. Although they differ chemically, all appear to be effective as a result of their ability to inhibit the production of biologically active prostaglandin. Indomethacin was first shown to have an effect in ureteric and biliary colic by Holmlund and Sjodin (1978).

The aim of this study was, firstly, to compare the pain-relieving effect of intravenous Avafortan (Asta-Werke, Germany) with that of intravenous indomethacin (Indocid) and intramuscular diclofenac (Voltaren) and, secondly, to observe whether a further injection of prostaglandin synthetase inhibitors would still give significant pain relief when compared with antispasmodic analgesics in the case of patients who required a second injection for complete pain relief.

## Patients and Methods

The series comprised 153 patients with the diagnosis of acute renal colic, based on history, clinical, urinary and radiological examination. Eight patients were excluded because of missing data. In a 2-week prospective randomised study, patients received either 50 mg intravenous indomethacin, or 50 mg intramuscular diclofenac or 4 ml intravenous Avafortan (camylofine bis, sodium phenyldimethyl-pyrazonolone-methylamino-methane sulphonate). The latter has a papaverine-like action and is used in cases of biliary and urinary tract colic.

Pain relief was rated as "no relief", "partial relief" and "complete relief". It was anticipated that the use of an analogue visual scale for assessment of pain relief would be difficult because most of our patients are expatriates with diverse ethnic and social backgrounds.

The pain-relieving effect of the drug was assessed 10, 20 and 30 min after injection. After 30 min, patients who had obtained no relief or only partial pain relief, and who required more analgesics, were offered a second injection of the same drug. Reassessment was continued at 10-min intervals for another 30 min. If the pain persisted 30 min after the second injection, the patient was given intravenous pethidine and admitted to the ward.

Randomisation was judged effective because there were no statistically significant differences

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**Table 1** Age, Sex and Pain Distribution

| | *Avafortan (n=54)* | *Indocid (n=44)* | *Voltaren (n=47)* | *Total (n=145)* |
|---|---|---|---|---|
| Age (years) | | | | |
| (SD) | 33.4±9.2 | 35±8.6 | 33.7±8.5 | 33.9±8.8 |
| Range | 13–50 | 21–61 | 14–53 | 13–61 |
| Sex | 48 M/5 F | 41 M/3 F | 42 M/4 F | 131 M/ 12 M |
| Pain | | | | |
| Severe | 26 | 20 | 17 | 63 |
| Moderate | 28 | 24 | 30 | 82 |

between the patients in terms of age, sex or severity of pain (Table 1).

Differences between means were assessed by Student's *t* test and analysis of variance. Differences in frequencies between groups were analysed with the $\chi^2$ test and Fisher's exact probability test. Significance levels of $P<0.05$ were set (2-tailed).

## Results

Following the first injection, patients receiving intravenous indomethacin had the highest complete pain relief rate (84.1%). In the intravenous Avafortan group the rate was 83.3%. This difference was not statistically significant. The intramuscular diclofenac group had the lowest complete pain relief rate (66%) (Fig. 1). There was a statistically significant difference between the indomethacin and diclofenac groups ($P<0.01$) and between the Avafortan and diclofenac groups ($P<0.05$).

After the first 10 minutes, no patient in the diclofenac group had partial pain relief compared with 11 patients given Avafortan (20%) and 5 given indomethacin (11%) ($P<0.01$ and $<0.05$ respectively). At 20 min, there was no significant difference in the number of patients experiencing partial relief in the Avafortan (59%), indomethacin (54%) or diclofenac (53%) groups. Subsequently, more patients reported complete relief of pain (Fig. 1). At 30 min, 11 patients in the diclofenac group (23%) had partial relief of pain but required a second dose of the drug to obtain satisfactory relief compared with 3 (5.6%) and 3 (6.9%) patients in the Avafortan and indomethacin groups respectively.

Table 2 shows the distribution of the 32 patients who needed a second injection for complete pain relief. In the indomethacin group the rate increased from 84.1 to 95.4%, in the diclofenac group from 66 to 93.6% and in the Avafortan group from 83.3 to 92.5% (Fig. 2). In patients who did not experience satisfactory pain relief following the first injection, the second intramuscular injection of diclofenac resulted in more pronounced and significant pain relief compared with that following the second injection of Avafortan ($P<0.05$). However, the

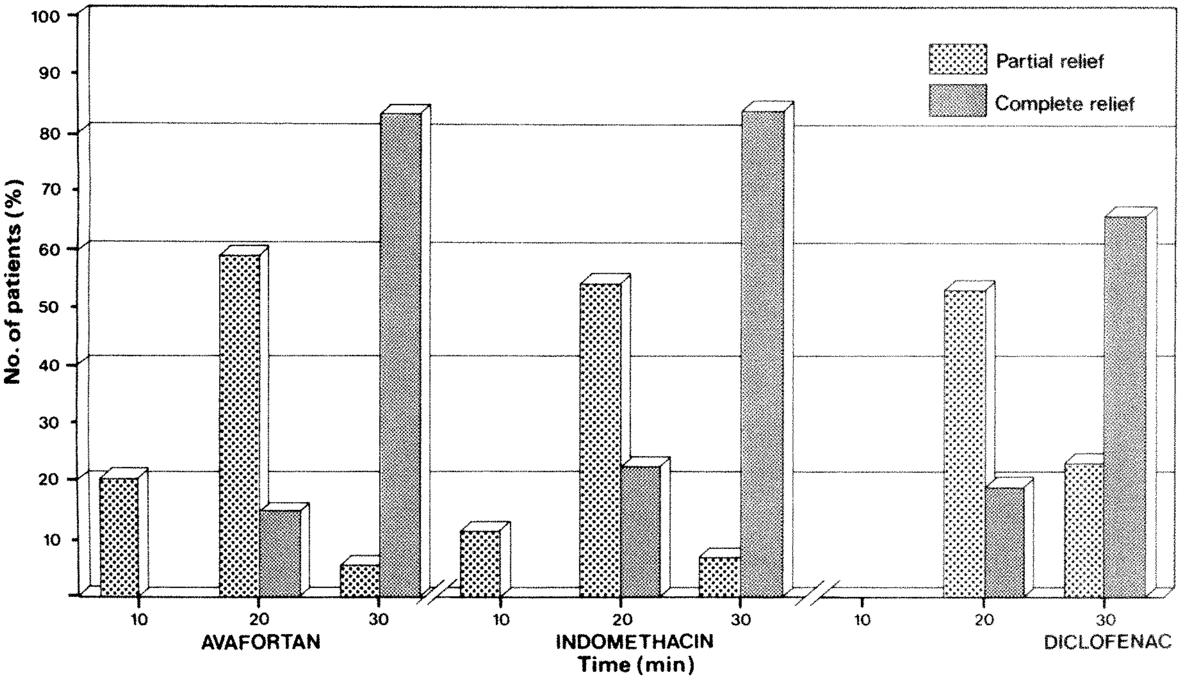

**Fig. 1** Response to first injection.

**Table 2** Patients Requiring a Second Injection

| *Drug* | *No relief (%)* | *Partial relief (%)* | *Total (%)* |
|---|---|---|---|
| Avafortan (n = 54) | 6 (11.1) | 3 (5.5) | 9 (16.6) |
| Indomethacin (n = 44) | 4 (9) | 3 (6.8) | 7 (15.9) |
| Diclofenac (n = 47) | 5 (10.6) | 11 (23.4) | 16 (34) |
| Total | 15 | 17 | 32 (22) |

difference between the outcome of the 3 drugs at the end of 60 min was not statistically significant.

Two patients (5%) from the indomethacin group, 3 (6%) from the diclofenac group and 4 (7%) from the Avafortan group needed pethidine and admission to hospital because they did not obtain complete pain relief after the second injection.

A drop in blood pressure and pulse rate occurred in all 3 groups of patients; there was no significant difference in the means.

There were no side effects in patients receiving intravenous Avafortan. Two patients in the indomethacin group developed nausea, 1 vomited and 1 complained of drowsiness. Another patient developed extensive petechial haemorrhage on the anterior aspect of his forearm after intravenous indomethacin; there was no indication of extravasation of the drug. Of the patients treated with diclofenac, 1 complained of nausea (which he had had before the injection) and 2 vomited after the first injection.

## Discussion

It appears that prostaglandin synthetase inhibitors should be given intravenously in order to achieve prompt pain relief. Persson *et al.* (1985), comparing intravenous Indoprofen with intramuscular oxycone—papaverine, established intravenous administration as the preferred route. When Khalifa *et al.* (1986) compared the pain-relieving effect of intramuscular diclofenac with that of intravenous pethidine and hyoscine butyl bromide, the latter preparation had a statistically higher success rate but also a higher incidence of side effects. The results following the first injection show that intravenous indomethacin compared favourably with intravenous Avafortan, while intramuscular diclofenac had the lowest complete pain relief rate.

The onset of analgesia was variable. At 10 min, more patients in the intravenous Avafortan group (20%) and the intravenous indomethacin group (11%) experienced partial relief of pain than in the intramuscular diclofenac group (0%). This difference probably arose because diclofenac was administered intramuscularly and therefore acted more slowly. At 20 min, however, the difference was not significant.

Sjodin *et al.* (1982) recorded the renal pelvic pressure in response to indomethacin in anaesthetised pigs and found that the pressure in an obstructed renal pelvis was further reduced after a

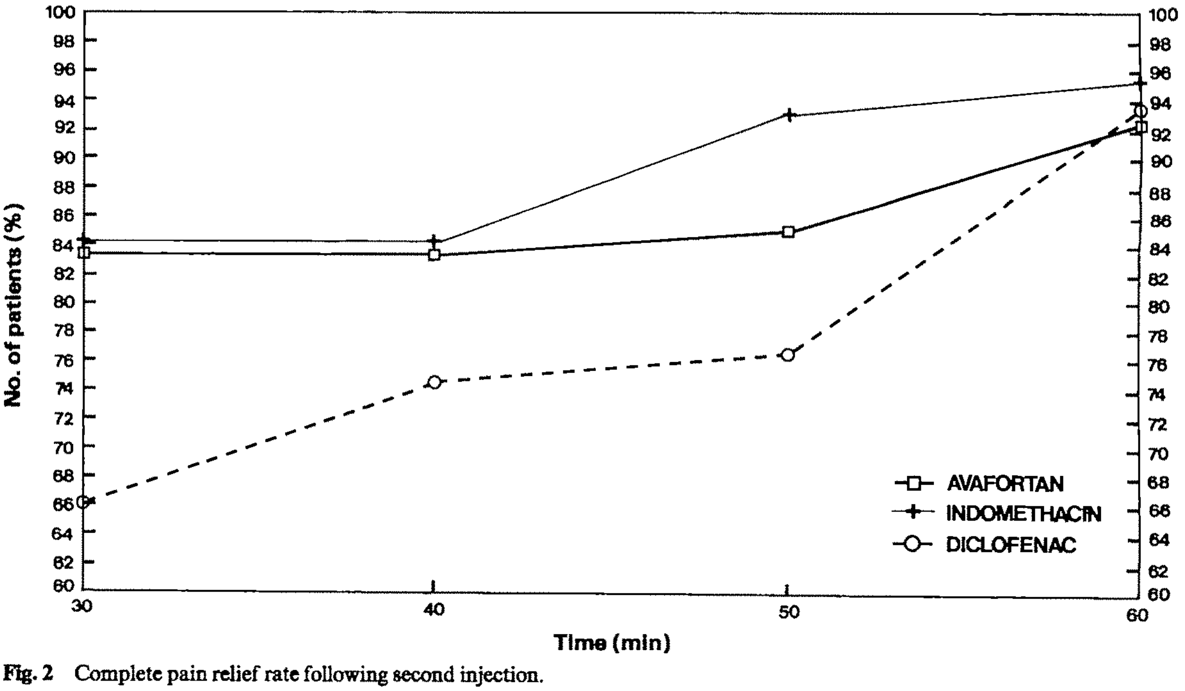

**Fig. 2** Complete pain relief rate following second injection.

second injection of indomethacin. The reduction in diuresis reached its maximum after 60 min.

The noticeably greater pain-relieving effect achieved by prostaglandin synthetase inhibitors after the second injection (whether given intravenously or intramuscularly) was presumably due to their cumulative effect in reducing renal pelvic pressure and further inhibiting the synthesis of prostaglandins which interfere with the mechanism of action of the antidiuretic hormone (Grenabo *et al.*, 1983).

Our results are in accord with those of Lundstam *et al.* (1982), who reported complete relief of pain in 70% of patients after 1 intramuscular injection of 50 mg diclofenac sodium and in 90% after a second injection. This effect was attributed to a reduction in the rise in intrapelvic pressure mediated by the release of prostaglandin in the kidney during ureteric obstruction.

Holmlund and Sjodin (1978) reported that 78% of their patients with acute renal colic experienced complete pain relief after intravenous indomethacin. This again is comparable to our results, as 84.1% of patients who received intravenous indomethacin had complete pain relief.

Prompt and adequate pain relief is the aim in treating acute renal colic. If the first injection of prostaglandin synthetase inhibitor fails to achieve this, a repeat dose of the same drug should be considered, for over 93% of patients in the indomethacin and diclofenac groups were pain-free when this was done.

Avafortan may affect a patient's reaction time and impair his or her ability to drive in traffic or to operate machinery. Further administration of the drug may intensify this effect.

Only 9 of 145 patients had to be admitted to the urology ward. The admission rate was lowest when prostaglandin synthetase inhibitors were used as first and second injections, although the difference was not statistically significant.

In the present study, Avafortan had no side effects. However, it contains dipyrone, which has been implicated as a causative agent in immune haemolytic anaemia, agranulocytosis and hypersensitivity reactions such as shock. We noted no serious side effects with prostaglandin synthetase inhibitors, although Jönsson *et al.* (1987) reported a 45-year-old man who developed a cold sweat, became unconscious and had a significant drop in blood pressure after the intravenous injection of 2 ml-10 mg indomethacin.

It has been shown that intravenous indomethacin is an effective alternative to intravenous Avafortan in treating acute renal colic, since it lacks the serious side effects of the latter preparation. Immediate pain relief is required in cases of acute renal colic and the intravenous route is therefore recommended. If the first injection of prostaglandin synthetase inhibitors fails to relieve the pain, a second dose should be considered before resorting to narcotic analgesics.

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# Evaluation of a Bladder Advancement Extension Graft Technique

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Summary—A bladder advancement extension technique was developed to provide a reliable method for creating an extra length of bladder in continuity, so that Boari flap and psoas hitch procedures, with or without the extension grafts, would reach sufficiently high routinely to permit these procedures to become the preferred practical options for accomodating significant proximal ureteric deficiencies or for replacing the whole of the ureter. In addition, an omentally supported bladder graft was established separately for use in a "retrieval" procedure should extension graft stenosis develop subsequently.

Of 10 dogs studied for 6 months, 2 required "retrieval" pedicled island patch grafts for stenoses at extension graft/upper ureteric junctions. Healthy urothelium with muscle in the walls was seen in grafts resting on their supporting omental beds. At the time of sacrificing, none of the operated upper tracts was obstructed.

Fortunately, the clinical circumstance of a longitudinal deficiency of the proximal ureter such that a spatulated, end-to-end anastomosis without tension is not possible, remains uncommon. However, when this does occur, considerable difficulties often arise in both short-term and long-term management.

Bladder advancement procedures by themselves may, in patients endowed with capacious, well vascularised bladders, enable uppermost ureteric defects to be bridged (Flynn *et al.*, 1979; Kromann *et al.*, 1986). However, the problem of the apex of the Boari flap or psoas hitch not reaching high enough, even with various mobilising and tension-relieving procedures, tempers enthusiasm for these approaches in such circumstances. In addition, even if it is possible to perform a high anastomosis, there is concern that the most superior part of the bladder might be ischaemic, with the potential problems of extravasation, fibrosis and subsequent obstruction. As a result, attempts to retain an unimpaired functioning ipsilateral kidney are usually achieved by renal autotransplantation or interposition of ileum (Chatelain, 1977; Blandy, 1986).

Since "design specific" urothelium is generally regarded as the most appropriate epithelium for urine, and because of the disadvantages associated with transuretero-ureteric anastomoses, ileal interposition and renal autotransplantation (Tanagho, 1975; Bazeed *et al.*, 1983; Bodie *et al.*, 1986; Ranch *et al.*, 1989; Waters *et al.*, 1989) experimental studies were undertaken to investigate the role of omentally supported autologous partial thickness bladder grafts interposed as replacements of excised segments of ureters. The best results were obtained using grafts on previously established omental pedicles, all grafts remaining healthy and viable at 12 months (Gardiner *et al.*, 1982, 1984, 1988).

Unfortunately, there are a number of disadvantages in the interposition of bladder grafts in ureters. Firstly, this technique constitutes a considerable departure from, and is not complementary to, currently used operations. Secondly, multiple procedures lack appeal from a medical aspect as well as a litigious point of view. (Smith, 1988). Thirdly, endoscopic correction of stenoses following interposed bladder graft techniques would probably be more difficult than after bladder advancement in continuity procedures. Fourthly, hyperactive ureters above and below interposed acontractile grafts might result in long-term clinical

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problems—especially for patients prone to develop calculi.

Following a separate study, in which a continent cystostomy using autologous bladder with omentum was developed in dogs (Gardiner and Samaratunga, 1989) and then used successfully in humans (Gardiner, unpublished data), further experiments were undertaken for replacing ureters. These incorporated adaptations acquired from the continent cystostomy work which were integrated with the established surgical procedure of Boari flap.

The aim of this study was to develop an operative approach for replacing the whole of the ureter with autologous urothelium which would serve as an adjunct to the Boari flap and/or psoas hitch procedures so that, with or without the extension graft technique, they would be the most appropriate methods for managing *all* ureteric defects. An additional aim was to make provision for methods which would facilitate both endoscopic and open surgical correction of any stenoses that might develop subsequently.

## Materials and Methods

Fourteen dogs were involved in the study, but 4 were excluded. In 1 animal the stent could not be found at the planned time of removal at 4 weeks. The other 3 were sacrificed prematurely because they were constitutionally unwell, with vomiting and dehydration at 4, 5 and 5 days respectively following the initial procedure. The remaining 10 dogs were sacrificed 6 months after the first operation by intravenous infusion of pentobarbitone sodium (Lethobarb) 325 mg/ml.

Anaesthesia was induced by intravenous thiopentone sodium (28 mg/kg) and maintained with a fluorothane/nitrous oxide mixture following premedication with intravenous atropine (0.6 mg) and droperidol (1 mg/kg). An infusion of normal saline, together with gentamicin (60 mg/day) and ampicillin (0.5 g), was administered per-operatively and continued for several days. This was followed by amoxicillin (0.5 g orally) for 7 days. Analgesia was provided by flunixin meglumine (25 mg/dog) and metoclopramide hydrochloride (10 mg/dog) was given subcutaneously for nausea.

All 10 dogs had 2 operations via midline transperitoneal incisions, the second operation being for stent removal 3 to 4 weeks after the definitive procedure. At the first operation, the uppermost part of the left ureter was dissected from surrounding structures, with longitudinal vessels under-run to minimise their possible contribution to graft viability. A Boari flap, directed upwards and to the left, was fashioned. From this a tubularised graft of mucosa, lamina propria and superficial muscle was raised over a fenestrated Silastic stent with an outside diameter of 0.5 cm. Freeing the graft was accomplished by a combination of scissor distraction and sharp dissection commencing at the base of the flap and working upwards. During tubularisation, the graft was stretched longitudinally by a number of 5/0 sutures apposing the dissected edges and extending deeply to include the outer wall of the stent, to ensure that the graft would stay stretched and not "concertina". Thus the length of the tubularised graft exceeded that of the bed from which it came.

Two of the dogs excluded from the study developed pressure necrosis of those parts of the grafts covering the upper shoulders of the stents, resulting in urinary extravasation and vomiting. These animals were sacrificed and, in subsequent experiments, stent shoulders were shaved and the kidney rotated, then fixed laterally, to lessen the likelihood of pressure necrosis of the graft at the point of curvature into the kidney. In addition, a smaller fenestrated stent (outside diameter 2.16 mm) was fed through the outer stent to make the upper anastomosis easier since the untrimmed outer stent was larger than the uppermost part of the ureter. The proximal ureter was spatulated and the anastomosis effected with interrupted 5/0 Maxon sutures (Figs 1–3).

Following anastomosis, the graft area was wrapped with mobilised omentum which was fixed in position with sutures. In addition, a separate thin tongue of omentum was directed to the gutter formed after closing the first layer of mucosa, lamina propria and superficial muscle of the bladder. The omentum was fixed with interrupted sutures to ensure viability for a pedicled "island" graft of bladder wall should this be required for a subsequent retrieval procedure (Fig. 4).

All 10 dogs had indwelling catheters for 4 days following the first operation in an attempt to minimise post-operative extravasation. The catheters and drainage bags were protected by special jackets to prevent the dogs from removing them. In these studies all procedures involved left upper tracts, the right tracts remaining untouched and serving as controls. The wounds were closed in layers, Maxon (polyglycolide-trimethylene carbonate) sutures being used throughout. Yeates drains, sited below skin level to prevent dislodgement, were removed after 7 days.

Retrieval procedures were planned for those dogs

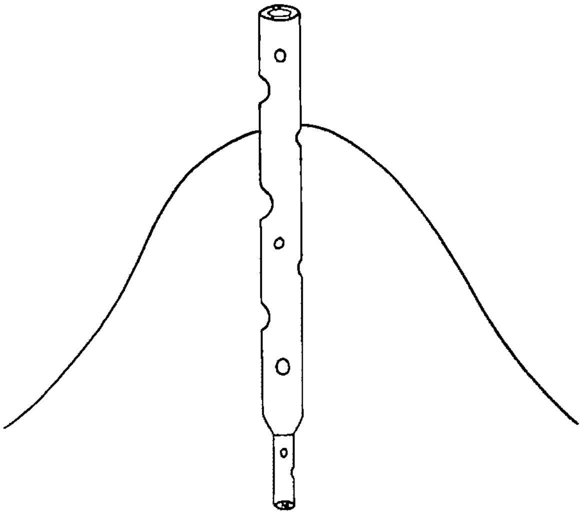

**Fig. 1** Fenestrated Silastic tubes laid on the Boari flap. Note the shaved "shoulders" of the outer tube adjacent to where the inner tube protrudes.

which developed ureteric obstruction on the graft sides diagnosed by intravenous urograms (IVUs). These operations involved isolation of a graft of bladder, on the previously established omental pedicle, to form an island patch graft to bridge a stenotic area and thus relieve obstruction; 8 F feeding tubes served as stents in the retrieval procedures and were removed 1 month later.

Intravenous urograms were planned for 8 weeks after the operation, 4 weeks after stent removal, at 4 months and then again at 6 months. Bacteriological examination of urine was undertaken at the time of stent removal and sacrificing. Specimens were fixed in formalin and paraffin embedded prior to sectioning for histological examination.

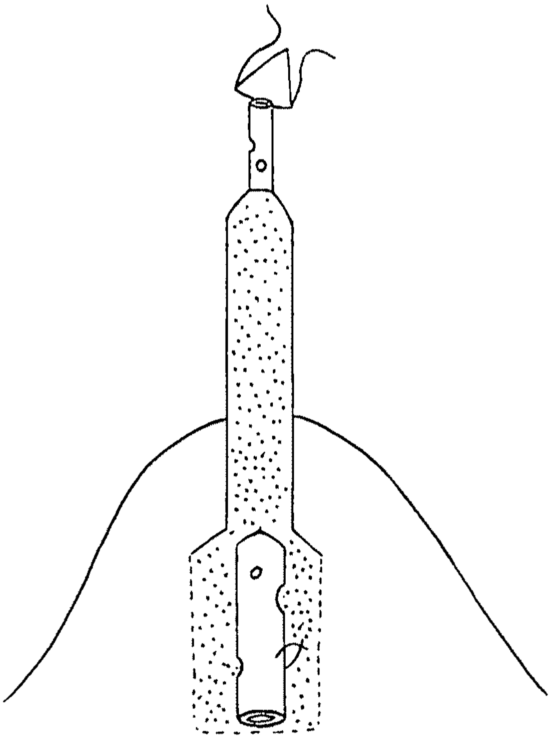

**Fig. 3** After a sufficient length of tubularised graft has been fashioned, the tubing is rotated 180° to enable insertion of the inner tube into the spatulated opening of the uppermost ureter. A vertical incision is made in the base of the pedicle graft so that the uncovered outer tubing may be brought through to rest on the donor site to which it is fixed. The donor site is left to urothelialise.

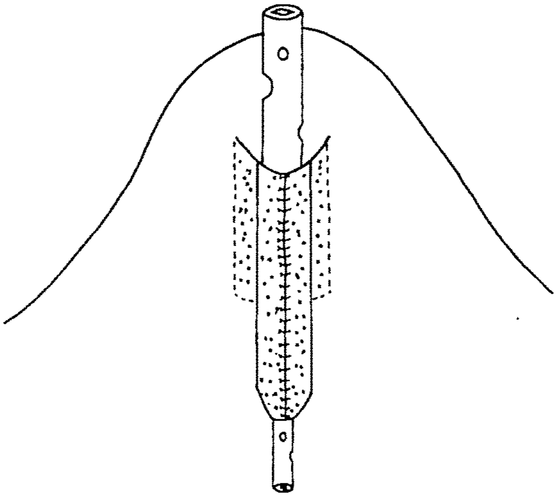

**Fig. 2** Partial tubularisation of the outer tube with stretched pedicle graft of mucosa, lamina propria and superficial muscle so that the length of the graft is longer than the donor site (exposed donor site and tubularised graft are stippled).

## Results

The radiological appearances were very acceptable at 2, 4 and 6 months (Fig. 5) (Table). On the basis of their radiological findings, 2 dogs required retrieval procedures. At these operations, the bladder was opened and an 8 F feeding tube advanced to the level of obstruction. In both cases stenosis had developed at the graft/upper ureteric junction and a mobilised island patch of bladder graft on its separate omental pedicle was anastomosed to the dilated ureter above and healthy bladder advancement extension graft below. In dog 3, this procedure was performed 11 weeks after the

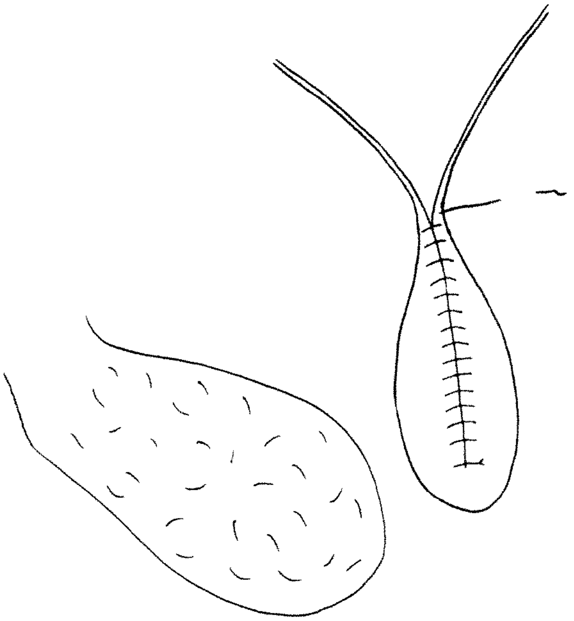

**Fig. 4** At the lower part of the cystotomy, mucosa lamina propria and superficial muscle are sutured in 1 layer. The edges of the deep muscle are separated sufficiently for a tongue of omentum to be placed, then sutured, at this site to form an established island pedicle graft for a "retrieval procedure" should this be required.

first operation and the IVU at 6 months showed minimal dilatation only (Figs 6 and 7). In dog 10, however, severe ureteric obstruction was not evident until 16 weeks, when a pedicled island patch graft was anastomosed. The IVU 2 months later demonstrated persisting pronounced pelvicaliceal dilatation. There was no delay in function, however, and an 8 F feeding tube passed easily from the bladder to the kidney at the time of sacrificing in both this dog and dog 5 (the other with pronounced pelvicaliceal dilatation at 6 months). This latter dog had purulent urine with macroscopic evidence of both upper and lower tract florid infection at this time.

Bacteriological evidence of urinary infection was present in suprapubic aspirates from dog 3 at 16 weeks (when the feeding tube stent was removed following the retrieval procedure), dog 5 at 6 months and dog 10 at 6 months. The organisms cultured were *Acinetobacter calcoaceticus* from dog 5 and *Enterobacter cloacae* from the other 2. In all 3 cases there were increased numbers of white cells in the urine.

Macroscopically, grafts on their omental pedicle beds appeared paler than the bladders whence they came. Histologically, healthy urothelium was present with an abundance of viable muscle, although there was an increase of collagen in the grafts compared with normal bladders (Fig. 8). Graft, ureter, bladder and kidney from dog 5 were acutely inflamed with cystitis and ureteritis cystica and acute pyelonephritis. Graft donor sites were covered by urothelium with a slight increase in underlying collagen.

## Discussion

These experiments have demonstrated that the bladder advancement extension graft technique can provide an effective method for overcoming longitudinal defects in upper tract continuity too high to be addressed by a Boari flap or a psoas hitch alone. The ability of the grafts to stretch to twice the length of the donor sites enables this approach to accommodate deficiencies extending the entire length of the ureter. Furthermore, the availability of the retrieval options of advancing an "island graft" on a previously established omental pedicle

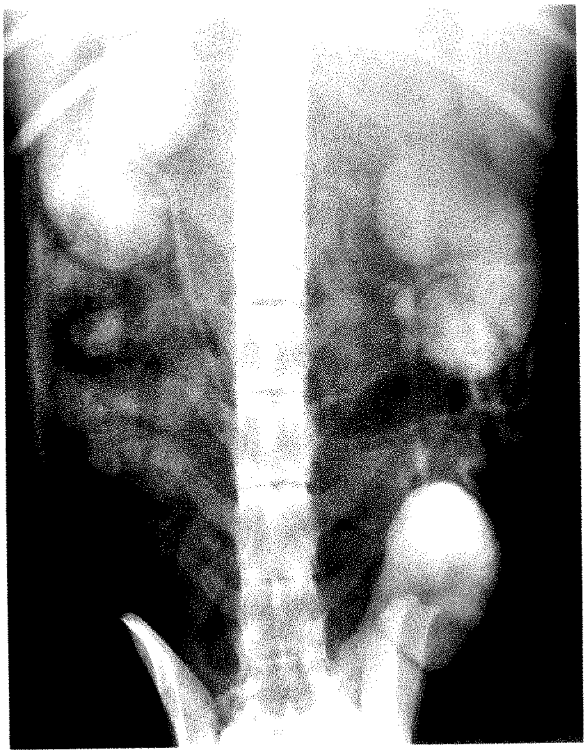

**Fig. 5** Normal appearance of upper tract at 6 months. Note the length of the extension graft above the Boari flap. In all instances the right upper tract was untouched and served as the control.

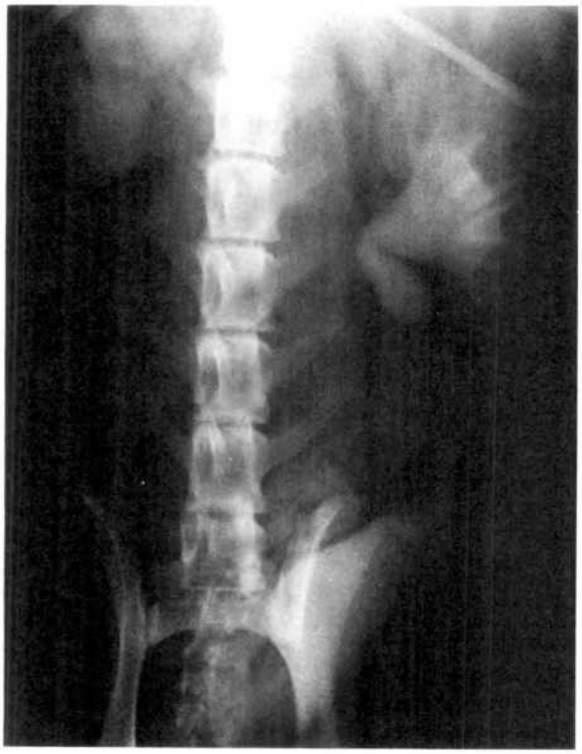

Fig. 6 IVU from dog 3 at 11 weeks, immediately before the "retrieval procedure", showing pronounced caliceal dilatation.

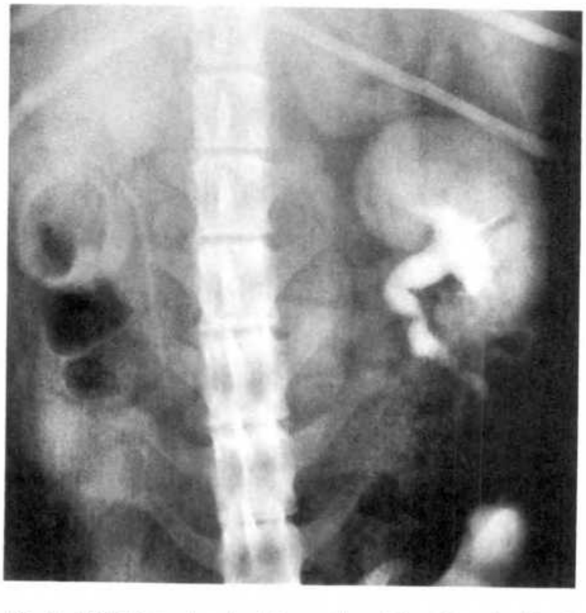

Fig. 7 IVU from dog 3 at 6 months with minimal caliceal dilatation and relief of obstruction.

**Table** Bladder Advancement Extension Graft. Radiological Details

| *Dog no.* | *IVU at 8 weeks* | *16 weeks* | *26 weeks* |
|---|---|---|---|
| 1 | M | – | M |
| 2 | N | – | N |
| 3 | Pro | M | M |
| 4 | M | – | N |
| 5 | M | – | Pro |
| 6 | M | – | M |
| 7 | M | N | N |
| 8 | Mod | M | M |
| 9 | M | M | M |
| 10 | M | Pro* | Pro |

N = normal. M = minimal dilatation. Mod = moderate dilatation. Pro = pronounced dilatation. Non = non-functioning.
* Time of retrieval procedure at 11 and 16 weeks respectively.

and the ready accessibility of transvesical endoscopic correction enhance the appeal of this approach.

In only 2 instances (dogs 3 and 10) were retrieval island patch bladder grafts required to correct discrete stenoses at upper extension graft/ureteric junctions. Although obstruction was relieved, the retrieval procedure was too late to reverse parenchymal damage caused by obstruction in the latter. However, the IVU at 6 months from dog 3 showed considerable improvement (Figs 6 and 7).

None of the operated upper tracts was obstructed at 6 months. This was confirmed in the 2 radiological failures, dogs 5 and 10, by the easy passage of an 8 F feeding tube from bladder to kidney at the time of sacrificing. Dog 5 had an acutely inflamed upper tract due to a florid urinary infection attributed to *Acinetobacter calcoaceticus*. Histologically, pronounced cystitis and pyelo-ureteritis cystica were present, together with changes of acute pyelonephritis.

Great care was taken during the operative procedures to maximise viability by continually moistening grafts with saline to prevent drying (Hovnanian and Kingsley, 1966; Greenberg *et al.*, 1983). Although the special property of omentum for supporting grafts is well recognised (Turner-Warwick, 1976; Samson and Pasternak, 1979), there may have been some contribution from the Boari flap. Proximally, longitudinal vessels in the uppermost part of the ureter, which may have contributed to graft viability, were under-run, so that the success of these grafts' survival postoperatively was almost totally attributable to the blood supply provided by surrounding omentum.

Macroscopically, the extension grafts appeared

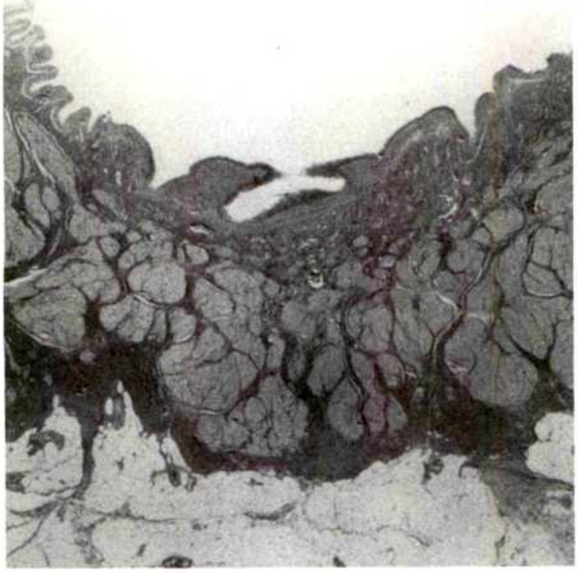

**Fig. 8** Low power photomicrograph of a transverse section of extension graft stained with haematoxylin van Gieson. Muscle bundles are prominent with underlying collagen supported by omentum. A normal urothelial lining is present.

paler than the Boari flaps from which they were fashioned, and from the retrieval island grafts used in dogs 3 and 10. As in our previous studies, the free omental wrappings supported viable urothelium, lamina propria and muscle. The choice of larger diameter stents than in the previous ureteric interposing graft studies seems to have been vindicated in that a graft stenosis sufficient to obstruct occurred in only 2 instances (Gardiner *et al.*, 1982, 1984).

Although a duration of 12 months was selected for radiological assessment in previous experiments, a shorter period was chosen for this study because of the absence of the urodynamic complicating factor of interposed acontractile graft segments between actively contracting ureters. In addition, perfusion pressure profiles were thought to be unnecessary since urography was considered adequate to exclude obstruction, and particularly since the main purpose of the study was to demonstrate a method for providing urothelial continuity from bladder to kidney which would enable preservation of renal function.

Monofilament polyglycolide-trimethylene carbonate sutures (Maxon) were used because this material was easier to handle than either woven Dexon (woven polyglycolic acid) or the chromic catgut sutures used previously. In most cases, Maxon sutures had disappeared by 6 months, although some persisted for several months in the bladder wall. These sutures are reported to be a little slower than Dexon to disappear from the urinary tract, which is consistent with our experience (Edlich *et al.*, 1987). There was no evidence of stone formation at the time of sacrificing (6 months). Experimental work in the rabbit, which is a better model for studying urolithogenesis, indicates that the likelihood of stone formation with Maxon is low, being equivalent to that for chromic catgut (Osterhage *et al.*, 1988).

This study demonstrates that the bladder advancement extension graft technique promises to be a simple complement to Boari flap and psoas hitch procedures when these manoeuvres are insufficient to accommodate the extent of a ureteric deficiency by themselves. The approach enables early surgical correction and provides a 1-stage technique which offers a high likelihood of success by itself, yet facilitates review procedures by both endoscopic and open surgery should they be required. Urothelial continuity is maintained using autologous urinary tract tissue, without renovascular disconnection, contralateral upper tract violation or incorporation of incompatible urodynamic segments. Thus the bladder advancement extension graft technique appears to be the logical adjunct to standard procedures for overcoming ureteric deficiencies.

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# Caffeine: Does it Affect your Bladder?

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Summary—Patients with symptoms of frequency and urgency often complain that their symptoms are exacerbated by tea or coffee. A series of 20 women with confirmed detrusor instability and 10 asymptomatic women were given 200 mg of caffeine citrate and urodynamic studies were performed. In the group with detrusor instability there was a statistically significant increase in detrusor pressure on bladder filling following administration of caffeine, but no difference in volume at first contraction, height of contraction or bladder capacity. Normal women had no abnormality on cystometry.

Patients with symptoms of urgency and frequency (particularly due to detrusor instability) often complain that these are exacerbated by drinking tea or coffee. Caffeine is a xanthine derivative occurring naturally in tea and coffee. It is known to cause a mild diuresis by acting on the renal tubules to increase renal blood flow and decrease sodium and water reabsorption from the distal tubule in a manner similar to that of thiazide diuretics (Maren, 1961). This may be the reason for the increase in urinary frequency. However, it has long been known that caffeine also acts on skeletal muscle to enhance the capacity for muscular work (Foltz *et al.*, 1942) and increases the resting tension of denervated muscle (Huidobro and Amenbar, 1942). It increases the release of acetylcholine and alters the translocation of intracellular calcium. Caffeine causes smooth muscle relaxation, particularly in the bronchi and vascular tree. Its effect on the detrusor muscle has not been studied and it is possible that it has a direct effect on the detrusor muscle, thus increasing detrusor activity.

We have investigated the effect of oral caffeine citrate on 20 patients with known detrusor instability and 10 asymptomatic women to determine whether there is a subjective or objective change in bladder function.

## Patients and Methods

Twenty patients with detrusor instability proven on urodynamic studies and 10 normal volunteers were asked to take part in the study. All patients with detrusor instability complained that their symptoms were exacerbated by caffeine containing drinks. They were asked to avoid such drinks for 24 h prior to the study. They then underwent routine twin-channel cystometry and uroflowmetry and were asked to attend for repeat urodynamic studies at least 2 weeks later. The delay was to eliminate any "learned response" altering their response to bladder filling. At this visit they were given 200 mg of caffeine citrate to drink. (A cup of instant coffee contains approximately 85 mg of caffeine (Rall, 1985). Caffeine citrate reaches peak plasma concentrations in 30 to 50 min and has a half-life of 3 to 4 h). Thirty minutes after the administration of the caffeine, urodynamic studies were repeated. The 10 normal volunteers were given 200 mg of caffeine citrate followed by cystometry 30 min later. They did not undergo urodynamics prior to entering the study.

## Results

Cystometric data for the 2 groups are shown in the Table. A paired *t* test was used to compare the results in patients with detrusor instability before

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**Table** Cystometric Data

| | *Without caffeine* | *With caffeine* | *Normal* |
|---|---|---|---|
| First desire to void (ml) (mean, range) | 148 (48–282) | 136 (36–234)* | 159 (80–252) |
| Bladder capacity (ml) | 378 (116–699) | 346 (100–537)* | 540 (290–830) |
| Volume at first contraction (ml) | 280 (80–590) | 245 (10–450)* | N/A |
| Height of maximal contraction (cm$H_2O$) | 32 (10–80) | 34 (10–70)* | N/A |
| Pressure rise on filling (cm$H_2O$) | 11 (0–25) | 17 (0–42)† ($P<0.03$) | 2 (0–5) |
| Pressure rise on standing (cm$H_2O$) | 11 (0–20) | 9 (0–32)* | 2 (0–3) |
| Maximum voiding pressure (cm$H_2O$) | 56 (30–120) | 37 (12–120)* | 22 (5–52) |
| Peak urinary flow rate (ml/s) | 27 (7–40) | 21 (5–36)* | 25 (10–45) |

* Not significant.
† Significant.

and after caffeine administration. This showed a significant increase in the detrusor pressure rise on bladder filling after caffeine administration compared with no caffeine administration ($P<0.03$). There was no difference in the first desire to void, the volume of first contraction, the height of the maximum contraction or bladder capacity.

The normal group showed no abnormality on urodynamic studies and in particular no low compliant rise on bladder filling. They reported no symptoms of urgency or frequency following the caffeine.

## Discussion

These results indicate that the increase in urgency and frequency noted after drinking caffeine-containing compounds may not be due purely to the diuretic effect of caffeine. An increased pressure rise during bladder filling indicates a decrease in bladder compliance and is likely to be responsible for the symptoms. This is probably a direct effect of caffeine on the detrusor muscle and suggests that caffeine has an excitatory effect on detrusor smooth muscle comparable to that described in skeletal muscle. This has implications in the treatment of patients with detrusor instability, particularly in those with a high consumption of tea and coffee.

Further studies need to be done on women with normal cystometry who complain of frequency after drinking coffee.

## Acknowledgements

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# Experience with a Simplified Technique for the Treatment of Female Stress Urinary Incontinence

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Summary—Over a 9-year period a simple procedure for the correction of stress urinary incontinence was performed in 86 consecutive patients, 31 of whom had failed a previous anti-incontinence procedure. Success was achieved in 81 cases (94%). Of the 5 failures, 2 were successfully treated with a repeat procedure. Operative time ranged from 14 to 49 min (median 27). The average hospital stay was 2 days. Because of its simplicity and reliability, this technique is recommended for the surgical correction of female stress urinary incontinence.

The cornerstone for the treatment of female stress urinary incontinence is the restoration of the bladder neck area from a position of dependency to one that will bring it high behind the symphysis pubis. The original retropubic urethropexy first described by Krantz *et al.* (1949) remains the best known operation. One of the disadvantages of this procedure, or any of its modifications, is the need for retropubic surgery and its possible complications. Equal success with the various endoscopic needle vesical neck suspensions has been reported, but most of these procedures require vaginal dissection in addition to a suprapubic incision to the rectus fascia. We describe a simplified needle suspension in which no vaginal dissection or large incisions are made.

## Patients and Methods

Between July 1979 and June 1988, 86 female patients with stress urinary incontinence were treated with a modified bladder neck suspension. The age range was between 28 and 90 years (average 56). Pre-operative evaluation included routine laboratory analysis, cystoscopy, and an intravenous urogram or renal ultrasound. Urodynamic studies were performed in 63 patients. Documentation of stress incontinence in all women was done by the classic Marshall test, both in the supine and standing positions. A total of 31 patients had undergone a previous unsuccessful anti-incontinence procedure; 14 had had a Marshall-Marchetti-Krantz vesicourethral suspension, 10 had anterior colporrhaphies and 7 a Stamey endoscopic suspension.

The procedure is carried out under either a general or a regional anaesthetic. Parenteral cephalosporin is given pre-operatively. The patient is positioned in the dorsal lithotomy position and routine preparation of the lower abdomen, perineum and vagina is carried out. The anus is draped out of the field and a 16 F catheter is placed in the bladder. By applying slight traction on the catheter, the bladder neck area is readily identified. All urine is drained from the bladder (this is important because keeping the bladder empty minimises the risk of perforating it with one of the needle passes). The labia minora are then sutured laterally and a weighted vaginal speculum is placed. Two small stab wounds are made suprapubically just above and lateral to the pubic bone. No attempt is made to dissect to the rectus fascia. A pair of double-pronged needles are then passed immediately behind the pubic bone into the vagina. During this manoeuvre the operator's middle finger retracts the urethral catheter medially and the index finger pushes the anterior vaginal wall upward, allowing the tip of the needle to emerge at both sides of the

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finger tips, thus inspiring proper placement. A quick cystoscopic examination is performed with both needles in place to ensure that there has been no bladder perforation. It is advantageous to move both needles at this time to verify their position. The needles are then threaded with 2 strands of either No. 1 hydroxyprolene or No. 2 Mersilene which have been centrally tied with a barrel knot (Fig. 1). Pulling on the needles, the sutures are transferred suprapubically where they are tied down with enough tension to see the bladder neck area elevate (Fig. 2). The stab wounds are closed with fine subcuticular absorbable sutures and covered with a bandage. No vaginal packing is required. A catheter is left indwelling for 24 h. A percutaneous cystostomy tube is placed at the end of the procedure and the patient is instructed on its use when discharged from hospital. If no spontaneous voiding ensues, the suprapubic tube is left unclamped for an additional 24 h, after which time it is clamped and unclamped at 4-h intervals, or when suprapubic discomfort occurs. Once the patient begins voiding, her residual urine is measured with the aid of the cystostomy catheter and when it is less than 90 ml the catheter is removed. If retention persists for more than 3 weeks postoperatively, the patient is taught intermittent self-catheterisation. Oral antibiotics are continued until the suprapubic catheter is removed and all patients are seen approximately 3 weeks later, when a vaginal examination and urine analysis are carried out.

## Results

All patients have been followed up annually in our out-patient incontinence clinic. If there is no leakage and voiding is unobstructed, the operation is considered successful. Of the 86 reported cases, a minimum follow-up of 6 months was available in all, while 57 had 5 or more years of follow-up by either clinic visits or direct telephone contact through a nurse clinician. The overall median follow-up was 27 months.

Of the 86 patients studied, 81 (94%) were rendered dry by this technique. One of the 5 failures occurred within 5 months of the initial procedure and the other 4 occurred after 27, 36, 41 and 60 months respectively. Two of these ladies underwent a repeat suspension and are currently dry. The remaining 3 refused any further surgical intervention and remained incontinent. The operative time ranged from 14 to 49 min (average 27) and hospitalisation ranged from 2 to 4 days (average 2) (Table 1).

Complications occurred in 6 patients (7%) (Table 2). One patient developed a superficial wound infection and was treated with drainage and another developed persistent urinary tract infection. Cystoscopy 4 months later revealed the presence of a

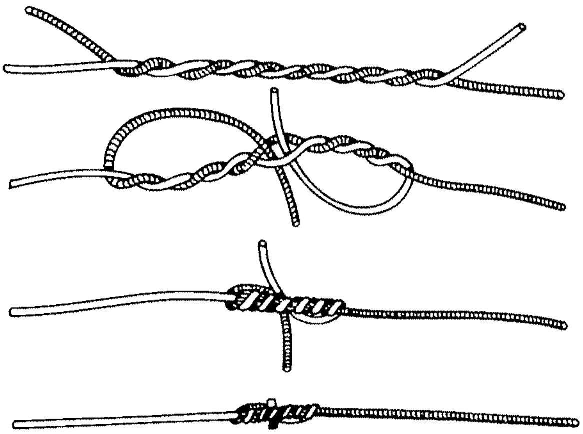

Fig. 1 Creation of double-barrel knot with either No. 2 Mersiline or No. 1 hydroxyprolene.

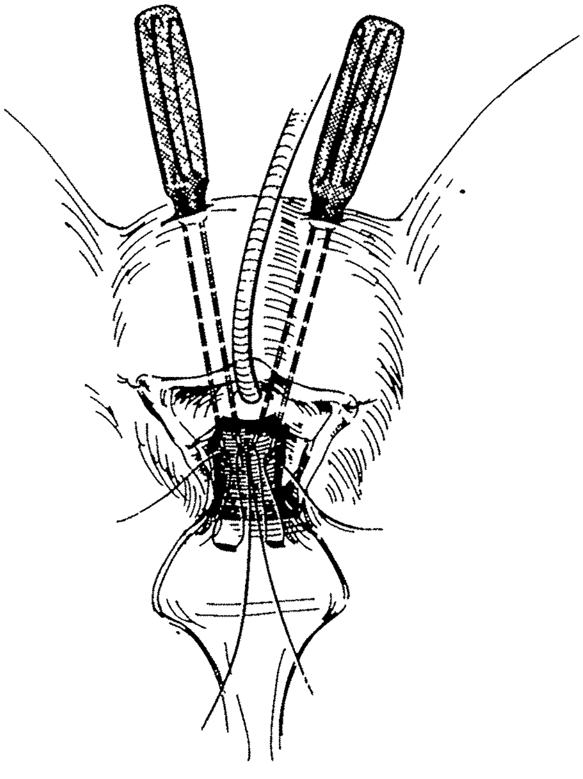

Fig. 2 The previously placed double-prolonged needles are threaded and the sutures transfixed suprapubically where they are tied.

**Table 1** Operative Results in 86 Patients

| | |
|---|---|
| Successful | 81 (94%) |
| Failures | 5 (5%)<br>2 repeat suspensions—successful<br>3 refused |
| Operative time (min) | Range 14–49 (average 27) |
| Hospital stay (days) | Range 2–4 (average 2) |

**Table 2** Complications

| | |
|---|---|
| Wound infection | 1 |
| Pelvic haematoma | 1 |
| Suture in bladder | 1 |
| Prolonged retention | 3 |

suture through the bladder which required removal. One patient developed a pelvic haematoma that was treated conservatively. In 3 patients, prolonged urinary retention over 3 weeks required intermittent self-catheterisation. Spontaneous voiding ensued within 6 weeks in 2 of these patients and the third required self-catheterisation for 7½ weeks.

## Discussion

The percutaneous approach for vesical neck suspension was first introduced by Pereyra (1959) and later redefined by Stamey (1973), thus establishing this procedure as safe and effective in the treatment of stress urinary incontinence in women. Since then, various modifications have been devised. Our procedure is based on a technique introduced by Cobb and Ragde (1978). The major difference is that we have excluded the need to perform any incisions or dissection in the vagina. The 2 small stab wounds in the lower abdomen facilitate the passage of the double-pronged needles; these avoid the need to make multiple needle passages and reduce the risk of inadvertently perforating the bladder. There is no need to use Dacron or Gortex bolsters because the bulky double-barrel knot acts as a pledget itself which later cuts through the vaginal mucosa and is then surrounded by a sheath of scar tissue that acts as an autologous buttress.

Incorporation of the vaginal sutures occurs quite rapidly, usually within 3 to 7 days as noted on colposcopic examination. These observations have been reported by Gittes and Loughlin (1987), who theorised that suspensory sutures work because a band of scar tissue forms between the resilient vaginal wall inferiorly and the rectus fascia and muscles superiorly, thus forming a 2-link chain on each side which connects the vaginal wall to the rectus fascia. When the individual increases the intra-abdominal pressure, as in coughing, etc, the chain-length holds and prevents the descensus and leakage of urine. The results presented here compare favourably with those of others (Gittes and Loughlin, 1987; Moralis and Van Cott, 1988). We believe that the fast operative time, high success rate, low morbidity and technical simplicity make this an ideal operation for the correction of stress urinary incontinence.

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# Urinary Continence in Spinal Injury Patients Following Complete Sacral Posterior Rhizotomy

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Summary—Complete sacral posterior rhizotomy was carried out in 15 spinal injury patients in conjunction with implantation of sacral anterior root stimulators. All patients were incontinent preoperatively and had video-pressure cystometry before and at regular intervals after surgery.

Detrusor hyper-reflexia was totally abolished in all but 1 patient following rhizotomy and 87% no longer require any form of incontinence appliance.

Deafferentation produced adverse changes in vesicourethral function and even when rhizotomy was complete, continence could not be guaranteed. The pre-operative state of the bladder neck and distal sphincter mechanism had an important bearing on future continence and those patients with a closed bladder neck and no previous sphincterotomy had the greatest chance of becoming continent after deafferentation.

The majority of patients in this series are now fully continent, representing a transformation in their quality of life; it is recommended, however, that to optimise the success of rhizotomy precise pre-operative evaluation and selection of patients are essential.

Sacral rhizotomy has been advocated for many years as a treatment for detrusor hyper-reflexia in the neurogenic bladder in an attempt to achieve urinary continence and protect the upper tracts from abnormally high detrusor pressures.

In ambulatory patients with neurogenic bladder dysfunction, complete sacral nerve rhizotomy is inappropriate because of adverse effects on the rectum, anal and urethral sphincters and the lower limbs. For this reason, selective neurectomy of the roots innervating the bladder alone has been suggested as the operation of choice in this group of patients (Tørring *et al.*, 1988), although long-term data have been disappointing owing to the recurrence of reflux detrusor activity (Torrens and Griffith, 1976; Rockswold *et al.*, 1978; Lucas *et al.*, 1988). In patients with complete supraconal spinal lesions, however, it is possible to perform total sacral neurectomy, giving patients the greatest chance of permanent continence without adverse effects. Munro (1945) and Meirowsky *et al.* (1950) were the first to describe this technique in spinally injured patients and although a number of other series have been reported, the long-term results have been poor (Manfredi and Leal, 1968; Toczek *et al.*, 1975, 1978; McGuire and Wagner, 1977; McGuire and Savastano, 1984).

Intradural sacral anterior root stimulators have been implanted in spinal injury patients since 1976 with the primary aim of improving bladder emptying (Brindley *et al.*, 1982). In recent years, however, the sacral posterior nerve roots of S2, S3 and S4 have been divided in some patients at the time of implantation in an attempt to achieve urinary continence (Brindley *et al.*, 1986). The anterior roots are left intact and subsequently stimulated within the implant. In this study we have looked in detail at the effect of complete sacral posterior rhizotomy on vesicourethral function in 15 spinal injury patients, together with implantation of sacral anterior root stimulators, in an attempt to predict those who are most likely to become continent and

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therefore to improve the selection of patients in the future.

## Patients and Methods

The study group included 15 patients (12 male, 3 female) with traumatic, complete supraconal spinal cord lesions (age range 20–53 years, mean 29.9). Two patients had cervical lesions, 12 thoracic and 1 lumbar.

All patients were incontinent of urine prior to sacral rhizotomy. Of the 12 male patients, 11 wore condoms and 1 had an indwelling catheter; of the 3 females, 2 had permanent catheters and 1 was on intermittent self-catheterisation and anticholinergics but remained incontinent. Five patients with lesions above T5 suffered significant autonomic dysreflexic symptoms induced principally by bladder distension.

All patients underwent pre-operative video-pressure cystometry at a filling rate of 10 to 20 ml/min, to confirm the presence of hyper-reflexic detrusor contractions and to document compliance, functional bladder capacity and residual urine. In addition, the state of the bladder neck and distal sphincter mechanism was assessed during filling and voiding and the presence of stress incontinence noted. Previous history of transurethral sphincterotomy was recorded. All methods, definitions and units conformed to the standards proposed by the International Continence Society. Those patients with small capacity bladders (<100 ml) had pre-operative intrathecal sacral root blockade using heavy Marcain (10 mg) to simulate posterior rhizotomy and hence to determine whether their increased bladder capacity after deafferentation would be sufficient to produce continence.

Surgery was carried out by the same consultant neurosurgeon (D.M.C.F.) at least 18 months following injury (mean 4.4 years). At operation the dura was exposed through a laminectomy from L3 to S1. Using the operating microscope, the sacral roots S2 to S5 were provisionally identified by their size and situation. The identification was confirmed by intra-operative stimulation of each root in turn, using a specially designed electrode and observing the detrusor and skeletal muscle responses. The roots were carefully separated into anterior and posterior divisions, causing the minimum possible trauma to the motor component. The separation was confirmed by stimulation and observation of motor responses. All posterior roots from S2 to S4 were than diathermied and divided. Deafferentation of S5 was also carried out if a detrusor response was obtained on stimulation. S5 and sometimes S4 roots were often too small to separate into their motor and sensory components and were therefore crushed *en masse* in the knowledge that anterior roots recover after crushing but posterior roots do not (Brindley *et al.*, 1988). All anterior roots were then placed in the implant intradurally and the operation continued as described by Brindley *et al.* (1988).

After 8 post-operative days, video-pressure cystometry was performed, during which the sacral anterior root stimulator was tested and urinary continence assessed. Urodynamics were repeated at 6 weeks and at regular intervals thereafter, depending upon the functioning of the sacral anterior root stimulator and the degree of continence achieved.

The 15 patients have been followed up over periods ranging from 2 to 17 months after sacral rhizotomy (mean 9.2 months).

## Results

### *Operative*

All 3 pairs of posterior nerve roots (S2, S3 and S4) were cut or crushed in 14 of the 15 patients and in addition S5 was crushed in 5. In a single patient, the S4 nerve roots bilaterally were left untouched because of their size, but we subsequently adopted a policy of crushing all roots that were too small to divide.

In 9 patients, S3 produced the maximum detrusor pressure at operative stimulation; S4 was the dominant root in 5 and in 1 case an identical response was seen with S3 and S4. There appeared to be an asymmetrical innervation to the detrusor, with both S3 and S4 on the right producing a greater intravesical pressure response in the majority of patients than the corresponding root on the opposite side.

### *Bladder*

All 15 subjects were shown to have detrusor hyperreflexia pre-operatively and 11 of them demonstrated some degree of detrusor-sphincter dyssynergia. After posterior rhizotomy, dyssynergia was abolished in all patients and only 1 had persistent reflex detrusor activity. This single patient was the one in whom the S4 roots were neither cut nor crushed and although he underwent further deafferentation at the level of the conus medullaris, he has persistent reflex activity and still needs to wear a condom.

Functional bladder capacity was increased in every patient by at least 140 ml (range 140–680, mean 404) (Fig.). Using a paired *t* test, this was shown to be a highly statistically significant increase ($P<0.00001$). Bladder compliance was normal in all patients pre-operatively, but at the first urodynamic assessment 8 days after rhizotomy, 6 patients had abnormally low compliance with opening of the bladder neck early in filling and subsequent stress incontinence. After 3 months only 1 of these had persistently reduced compliance and follow-up at 9 months revealed stress leakage at volumes >300 ml. Every patient who had initial poor compliance had a small capacity bladder before deafferentation (<200 ml) except for the 1 patient whose bladder has remained hypocompliant.

All patients were incontinent of urine before deafferentation and required some form of incontenence appliance. After sacral rhizotomy 13 patients (87%) no longer require any appliance and 11 (73%) are totally dry (Table). The 2 patients who are "drip dry" are now both taking ephidrine (15–30 mg *tds*). This has improved their continence sufficiently for them to manage without appliances, although both have some degree of stress incontinence on maximal physical exertion. Two of the patients who are now totally dry had some stress leakage initially but this was treated successfully with ephidrine. Of the 2 patients who are still incontinent day and night, 1 has persistent reflex detrusor activity and 1 has gross stress incontinence.

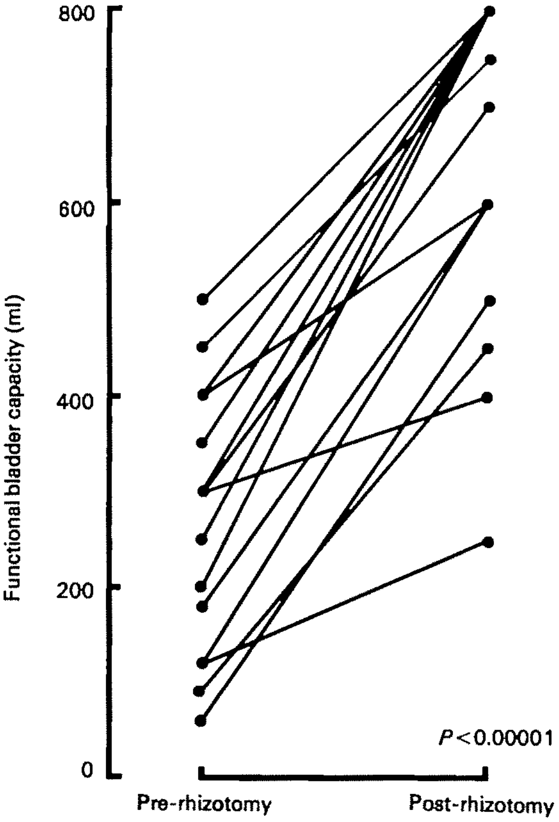

**Fig** Increased functional bladder capacity following complete sacral deafferentation.

**Table** The Effect of Complete Sacral Rhizotomy on Urinary Continence

| | *Dry* | *"Drip dry"* | *Wet* |
|---|---|---|---|
| Before rhizotomy | 0 | 0 | 15 |
| After rhizotomy | 11 | 2 | 2 |

Dry = Fully continent day and night.
"Drip dry" = Min. stress incontinence day and night.
Wet = Incontinent day and night requiring incontinence appliance.

The state of the bladder neck on video-pressure cystometry prior to sacral rhizotomy appeared to have some bearing on subsequent continence. Of the 4 patients who had an open bladder neck at rest pre-operatively, 3 were incontinent following deafferentation and of the 11 patients with a closed bladder neck pre-operatively, 10 were subsequently continent. The 1 patient in the latter group who was incontinent had had 2 previous transurethral sphincterotomies. One other patient in this series had a sphincterotomy with a closed bladder neck prior to rhizotomy and he is now fully continent. In the 5 patients who developed some degree of stress incontinence after deafferentation, video-pressure cystometry showed them to have permanently open bladder necks at volumes >150 ml. Four of this group have improved with ephidrine and 1 is still grossly incontinent, requiring a condom.

All 3 female patients are now fully continent and no longer require any form of catheterisation. They all had closed bladder necks before and after surgery with large increases in functional bladder capacity and normal compliance.

The 5 patients with autonomic dysreflexia have had total relief of symptoms after sacral rhizotomy.

All patients in this series pre-operatively defaecated reflexly, using stimulant solutions or suppositories. Following deafferentation, we found that reflex bowel activity was abolished in every patient, therefore requiring the use of manual evacuation for bowel emptying.

Reflex erections were also lost in every patient after rhizotomy.

## Discussion

In this series, 87% of patients are acceptably continent and no longer require an incontinence appliance; 73% are totally dry throughout the day and night. Of the 14 patients in whom reflex detrusor contractions were abolished, there has been no evidence of recurrent activity. Previous studies of selective sacral neurectomy have shown varying degrees of recurrent hyper-reflexia (Diokno *et al.*, 1977; Toczek *et al.*, 1978; Lucas *et al.*, 1988) and in one series activity recurred in all patients after 1 year (Opsomer *et al.*, 1984). It is suggested that these recurrences are due either to the development of alternative reflex pathways along surviving roots or to the sprouting of alpha-adrenergic nerve terminals at the bladder base (Sundin *et al.*, 1977). If we are aiming to achieve permanent continence, therefore, complete sacral neurectomy must be the operation of choice and although in this series we have left the anterior roots intact, in terms of interruption of the reflex detrusor pathways our neurectomy is complete.

Continence in our patients depended not only upon abolition of detrusor hyper-reflexia but also upon normal bladder compliance and a competent outflow tract. We observed a reduction in compliance in a number of patients, lasting for about 6 weeks after deafferentation, and in 1 patient there was persistent hypocompliance. Pre-operatively, despite having reduced bladder capacities, all of these patients had normal compliance. It is possible to explain these temporary changes as an entirely mechanical effect of stretching a previously contracted bladder wall. However, there may also be a neural component, as a consequence of deafferentation, particularly in the patient in whom hypocompliance has persisted.

There is no doubt that posterior rhizotomy has an effect on the distal sphincter mechanism and bladder neck. The patients with temporary poor compliance opened their bladder necks passively early in filling as the detrusor pressure rose. Excluding these patients, a further 5 developed permanently open bladder necks following rhizotomy and although 4 have improved considerably on ephidrine, 1 still has gross stress incontinence and requires a condom and leg bag. In addition to abolishing reflex striated muscle activity of the sphincters and pelvic floor, posterior rhizotomy must also have some effect on the smooth musculature of the distal sphincter mechanism and bladder neck, although some activity must be maintained for these patients to be continent at all. McGuire and Savastano (1984) noted that administration of an alpha blocker after complete rhizotomy virtually eliminated any urethral closure pressure. This would indicate that the sympathetic innervation to the smooth musculature remains intact and must therefore contribute to continence after posterior rhizotomy. We found that if the bladder neck was closed pre-operatively the patient would almost certainly be continent after deafferentation, although a previous transurethral sphincterotomy probably makes this less likely. An open bladder neck prior to rhizotomy, regardless of previous sphincterotomy, meant that the patient had a high chance of being incontinent. We have no patient in this series who pre-operatively had an open bladder neck and a sphincterotomy because the possibility of future incontinence would be unacceptably high.

All 3 females in this series are fully continent following deafferentation and no longer require any form of catheterisation. They did particularly well post-operatively, with large increases in functional bladder capacity, closed bladder necks and normal compliance. Female patients with hyper-reflexic bladders require either permanent catheterisation or anticholinergic therapy with frequent intermittent self-catheterisation. These patients therefore have a lot to gain from sacral rhizotomy if it is successful. Although the number of females in this series is small, it is tempting to suggest that they do better than male patients and we are now recruiting an increasing number of females to observe the effect of deafferentation on vesicourethral function and to determine whether they do indeed do better than males and why this should be so.

It is difficult to explain why reflex detrusor activity persisted in 1 patient despite a second rhizotomy at the conus medullaris. Deafferentation at this level is anatomically easier and more accurate than at the sacral roots themselves and it is therefore unlikely that any sensory fibres remain following surgery. This brings into question the concept of Bell (1811) and Magendie (1822), who proposed that dorsal roots contain sensory axons and ventral roots motor axons. It is possible that ventral roots might carry some afferent fibres, a theory supported by Coggeshall *et al.* (1975), who found unmyelinated axons in human anterior roots.

The potential disadvantages of posterior rhizotomy are loss of sacral sensation and loss of reflex bowel and erectile activity. The first of these is not relevant in our series as all patients had complete spinal lesions. Reflex defaecation is always abolished, necessitating the use of manual evacuation, but this is invariably quick and easy and is in most patients supplemented by the use of the stimulator for evacuation. Loss of reflex erections can be a problem in some patients as implant driven erections are not always attainable or sustainable. It might be possible in the future to preserve the S2 posterior nerve roots in the hope of retaining reflex erectile activity, although the effect of this on recurrent detrusor hyper-reflexia is not known.

In summary, complete sacral posterior rhizotomy is an effective treatment for urinary incontinence in spinal injury patients, with no evidence of recurrent detrusor activity during the period of the study. However, it is important to be aware that deafferentation can produce adverse changes in vesicourethral function and even if rhizotomy is complete, continence cannot be guaranteed. In addition, we have found that the pre-operative state of the bladder neck and distal sphincter mechanism has an important bearing on future continence. Provided these factors are considered when selecting patients for rhizotomy, the incidence of urinary continence is high, reflecting a significant improvement in the quality of life for the spinally injured patient.

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# Histopathological Effects and Recovery Rate of Rat Bladders following Intravesical Instillation of Thiotepa, Doxorubicin and Mitomycin C

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Summary—A study was made of the local reactions and systemic effects induced by intravesical instillations of thiotepa, doxorubicin and mitomycin C in rats. The control group received normal saline. In the 1-dose short-term experiments, rats treated with doxorubicin and mitomycin C had a high incidence of chemical reactions, including congestion of the mucosa with methylene blue stain, increased bladder weight with oedematous changes either in the mucosa (doxorubian) or the muscle layer (mitomycin C), and infiltration of polymorphonuclear cells 3 days after instillation. These local changes disappeared within 10 days. In long-term experiments with weekly instillations of chemotherapeutic drugs, the rats showed no significant change in weight, methylene blue staining or mucosal congestion. A high percentage of pyuria and microscopic haematuria with submucosal/muscular fibrosis was noted in rats receiving doxorubicin or mitomycin C. A severe dysplastic change in the urothelium was noted in rats treated with mitomycin C. These results suggest that careful follow-up is required in patients receiving intravesical doxorubicin or mitomycin C because of possible severe side effects in the bladder.

Superficial bladder tumours represent the commonest form of transitional cell carcinoma (Cox *et al.*, 1969). They are generally amenable to local resection, either transurethrally or through open surgery. Survival is excellent, although recurrences occur in 50 to 80% of patients (Droller, 1980). Most recurrences are of a similar low grade and stage and are readily managed by repeated local resection. However, recurrences eventually become invasive in 15 to 25% of patients and require more aggressive therapy. Intravesical chemotherapy has become one of the most important methods used in the treatment of bladder cancer and several different agents are used. Intravesical instillations of thiotepa (Veenema *et al.*, 1962), doxorubicin (Jakse *et al.*, 1981) and mitomycin C (Mishima *et al.*, 1975) have been used for the treatment and prevention of recurrence in patients with superficial bladder tumours. The purpose of this study was to evaluate the histopathological effects and recovery rate of normal bladder following the intravesical application of these agents in rats.

## Materials and Methods

Three-month-old female Sprague-Dawley (SD) rats weighing 200 to 250 g were employed. They were bred and maintained in a pathogenic free environment.

Thiotepa (tespamin, N,N′,N″-phosphinothioylidynetrisaziridine; Sumitomo Pharmaceuticals Co. Ltd, Japan), doxorubicin (adriblastina, doxorubicin hydrochloride; Farmitalia Carlo Erba, Italy) and mitomycin C (Kogyo Co. Ltd, Japan) were used. They were dissolved in sterile distilled water to a concentration of 1 mg/ml. Normal saline solution was used as a control.

The rats were divided into 2 major groups including 1-dose short-term and 6-dose long-term treatment groups.

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In the short-term study, the rats were anaesthetised by intraperitoneal injection of sodium pentobarbital (65 mg/kg; Somnotol, Mississauga, Canada). On day 0, the perineum was cleansed and a no. 24 teflon urethral cannula was inserted. After emptying the bladder by compression, 0.5 ml of thiotepa, doxorubicin, mitomycin C or nomal saline was gently instilled into the bladder. The catheter was clamped by a silver clip and fixed on the tail by a tape. The rats retained the drug for the duration of anaesthesia, a period of approximately 2 h. On days 1, 2 and 3, rats from 4 groups were sacrificed; each subgroup contained at least 3 rats. Before sacrifice, the bladders were stained with 0.5 ml of 0.1% methylene blue for 10 min and then flushed with normal saline until clear for observation of mucosal damage (Gill *et al.*, 1983). The bladders were removed, checked for mucosal staining by methylene blue, degree of congestion, and weighed. The bladders were then divided into 2 portions, 1 being used for routine histological examination and the other frozen for later use. For histological examination the bladder tissue was formaldehyde fixed, paraffin embedded, sectioned and stained with a haematoxylin and eosin. Similar experiments were repeated at least 3 times in each group.

**Table 1** Serial Changes in Bladder Mucosa and Weight in Rats Receiving Instillation of Normal Saline, Thiotepa, Doxorubicin and Mitomycin C

| *Agent* | *Day* | *Mucosal stain by methylene blue* | *Congestion* | *Bladder weight* |
|---|---|---|---|---|
| Saline | 1–3 | – | – | – |
| Thiotepa | 1–3 | – | – | – |
| Doxorubicin | 1 | – | – | – |
| | 2 | ± | + | – |
| | 3 | – | + | ↑ (60.5%) |
| Mitomycin C | 1 | – | – | – |
| | 2 | + | ++ | ↑ (61.7%) |
| | 3 | ++ | +++ | ↑ (91.7%) |

To evaluate the recovery rate of bladder mucosa in the acute stage after 1-dose intravesical instillation of various drugs, 4 groups of rats were employed, each group containing 18 animals. After the initiation of therapy, the rats were sacrificed at 2-day intervals. The bladders were removed and processed using routine histological techniques and stained with haematoxylin and eosin.

In the 6-dose long-term study, the rats received weekly instillations of thiotepa, doxorubicin, mitomycin C or normal saline over a 6-week period. Three days after the last instillation they were weighed and urine was collected. Methylene blue staining and congestion of bladder mucosa were checked after removal of the bladder. The weight of the bladder was recorded and it was divided into 2 portions, with 1 being processed for histological examination in regular haematoxylin and eosin.

## Results

In the acute phase with 1-dose treatment (Tables 1 and 2), bladders from the normal saline and the thiotepa groups showed only mild submucosal oedema in the thiotepa group and this returned to normal within 4 days. The bladders from the doxorubicin group showed progressive congestion of mucosa grossly and an increase in weight. Under light microscopic examination, hydrolytic changes in the mucosal layer with marked submucosal oedema and infiltration of polymorphonuclear cells were noted; these changes returned to normal

**Table 2** Microscopic Changes and Recovery of Bladders in Rats Receiving 1 Instillation of Normal Saline, Thiotepa, Doxorubicin and Mitomycin C

| | | *Light microscopy* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Mucosa* | | *Submucosa* | | | | *Muscle* | | |
| *Agent* | *Day* | *Hydrolysis* | *Slough* | *Oedema* | *Congestion* | *PMN cell infiltrate* | *Granulation* | *Oedema* | *PMN cell infiltrate* | *Recovery (days)* |
| Saline | 1–3 | – | – | – | – | – | – | – | – | – |
| Thiotepa | 1–3 | – | – | + | – | – | – | – | – | 4 |
| Doxorubicin | 1 | + | – | + | – | – | – | – | – | |
| | 2 | + | – | ++ | – | – | – | – | – | |
| | 3 | + | – | ++ | + | ++ | + | – | – | 8 |
| Mitomycin C | 1 | + | – | + | – | – | – | + | – | |
| | 2 | + | + | + | ++ | + | – | + | ± | |
| | 3 | ++ | + | + | ++ | ++ | + | + | ± | >10 |

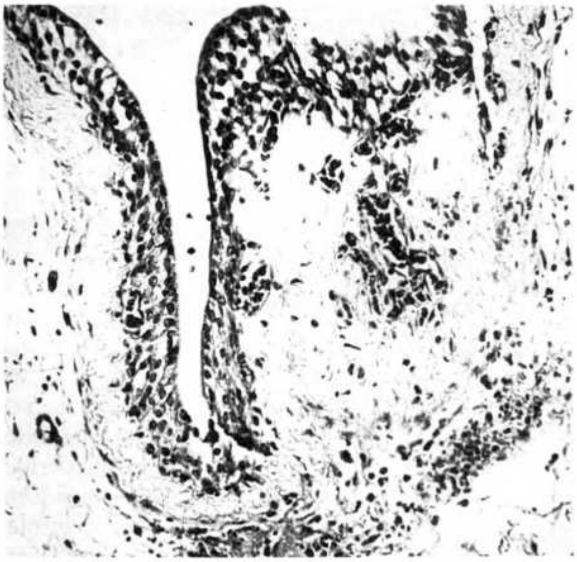

**Fig. 1** Hydrolytic and vesicular changes in urothelial cells with submucosal oedema in rats receiving 1 instillation of doxorubicin. (H and E × 200).

within 8 days (Fig. 1). The bladders from the mitomycin C group showed increased weight, marked congestion and mucosal staining by methylene blue due to epithelial damage. Microscopically, hydrolytic changes with sloughing of the mucosal layer, congestion of the submucosal layer with oedema, granulation reaction and infiltration of polymorphonuclear cells and oedema of muscle layer were noted. These effects did not return to normal within 10 days.

In the chronic phase with 6-dose instillations, no significant changes in body weight, bladder weight, congestion, oedema or mucosal staining by methylene blue were noted grossly, but a high incidence of haemapyuria was found in rats receiving doxorubicin or mitomycin C (Table 3). Microscopically, no marked changes occurred in the bladders following the instillation of normal saline, thiotepa or doxorubicin (Table 4). In 67% of the rats (12/18) receiving mitomycin C, there was focal or diffuse urothelial atypia (Fig. 2). In 22% (4/18) the bladder showed marked submucosal fibrous plaques in addition to inflammatory changes.

## Discussion

The intravesical instillation of chemotherapeutic agents is widely used in the treatment and prophylaxis of low grade, low stage urothelial carcinoma and carcinoma *in situ*. The present study was carried out to observe the effects of thiotepa, doxorubicin and mitomycin C on normal urothelium in rats.

The standard intravesical chemotherapeutic agent is thiotepa (Veenema *et al.*, 1962); this is an alkylating agent that exerts its therapeutic effect by producing cross-linking of nucleic acids and proteins. Its major toxic effect is myelosuppression due

**Table 3** Changes in Body Weight, Bladder Mucosa and Weight, and Urinary Examination in Rats Receiving Long-term Instillations of Normal Saline, Thiotepa, Doxorubicin and Mitomycin C

| *Agent* | *Body Weight* | *Bladder weight* | *Mucosal strain* | *Congestion and oedema* | *Haemapyuria (%)* |
|---|---|---|---|---|---|
| Saline | ↑ (21%) | – | – | – | 18 |
| Thiotepa | ↑ (16%) | – | – | – | 13 |
| Doxorubicin | ↑ (21%) | – | – | – | 67 |
| Mitomycin C | ↑ (21%) | – | – | – | 100 |

**Table 4** Microscopic Changes in Rat Bladders After Long-term Instillation of Normal Saline, Thiotepa, Doxorubicin and Mitomycin C

| | *Light microscopy* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Mucosa* | | | *Submucosa* | | | | *Muscle* | |
| *Agent* | *Hydrolysis* | *Slough* | *Dysplasia* | *Oedema* | *Congestion* | *PMN cell infiltrate* | *Fibrosis* | *Oedema* | *Fibrosis* |
| Saline | – | – | – | – | – | – | – | – | – |
| Thiotepa | – | – | – | – | – | – | – | – | – |
| Doxorubicin | ± | – | – | ± | + | – | + | – | – |
| Mitomycin C | ± | – | +++ | + | ± | + | ++ | – | ± |

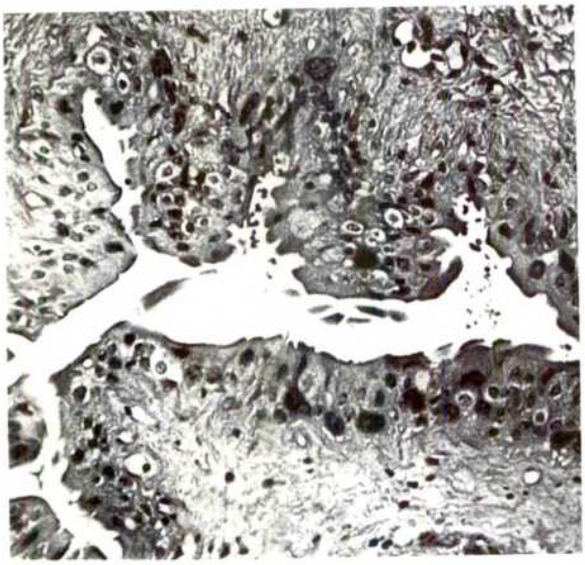

**Fig. 2** Metaplastic changes in urothelial cells in rats receiving long-term instillations of mitomycin C. (H and E × 200).

to its low molecular weight. Thiotepa was reported to have little or no adverse effect on normal bladder urothelium (Jones and Swinney, 1961; Huang, 1984). We found that it had no severe pathological effect on normal urothelium in the acute or chronic phase and the mild submucosal oedema which it did induce disappeared within 4 days.

Rasmussen *et al.* (1980) reported that repeated intravesical instillation of thiotepa produced mild hypertrophic and vesicular changes in normal urothelium. Friedman *et al.* (1988) found that 50% of the animals in the thiotepa groups showed an inflammatory reaction with mild urothelial hyperplasia. These changes did not occur in our study, possibly because of differences in the drug concentration and instillation schedule.

Doxorubicin acts primarily by inhibiting DNA synthesis of cells. Its use as a topical intravesical agent was reported by Pavone-Macaluso *et al.* (1984). The major adverse side effects included relatively marked chemical cystitis that in some patients progressed to permanent bladder contracture. It can induce generalised superficial inflammation and squamous metaplasia in the human bladder. Severe vocuolation and keratinisation were also seen in the urothelium of FANFT-fed rats receiving doxorubicin intravesically (Banks *et al.*, 1977). In the present study, hydrolytic, vacuolated cytoplasm and desquamated mucosa, with marked submucosal oedema and inflammation, were noted in the acute phase under light microscopy. These changes were reversible within 8 days. No squamous metaplasia or bladder contracture was noted in the long-term study, although mild submucosal fibrosis was found.

Significant findings in the rats treated with mitomycin C were marked hydrolysis and desquamation of the mucosa with severe congestion; inflammation of the submucosal layer was also noted in the acute phase. Urothelial dysplasia with submucosal fibrosis was noted in rats receiving repeated instillations of mitomycin C in addition to inflammatory changes. Murphy *et al.* (1981) demonstrated that when this agent was administered to mice fed with the carcinogen FANFT, an irritant effect on urothelium was produced, with exfoliation, degeneration and necrosis of bladder mucosal cells. Friedman *et al.* (1988) found urothelial atypia in 46% and submucosal fibrous plaques in 17% of rats treated with repeated instillations of mitomycin C weekly for 8 weeks and correlated this to the reduced bladder capacity seen in the clinical setting. Close follow-up and bladder biopsy may be needed to observe these changes attributed to mitomycin C or doxorubicin.

The high incidence of pyuria and haematuria in the doxorubicin and mitomycin C groups also related to their destructive effect on normal urothelium with subsequent inflammatory processes. Mitomycin C had a stronger local effect on the bladder than did doxorubicin. Further study will be focused on the carcinogenic effect of mitomycin C on normal urothelium in different dosages, schedules and duration of instillation.

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# Ten Cases of Transitional Cell Carcinoma of Bladder Causing Ureteric Obstruction

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Summary—A review was carried out on 10 patients with superficial transitional cell carcinoma of the bladder (Ta lesions) that were causing ureteric obstruction. Evidence of upper tract obstruction did not necessarily indicate deep invasion.

It is generally accepted that ureteric obstruction due to carcinoma of the bladder indicates deep invasion with a poor prognosis (Badenoch, 1965; Williams and Mitchell, 1973; Blandy, 1982; Bailey and Love, 1984). Blandy (1982) implied that if the ureter was obstructed, it usually meant that the muscle near to the ureteric orifice was involved, and hence the growth was pT2 or worse (UICC, 1978).

## Patients and Methods

A retrospective study was made of the case notes of patients with superficial tumours of the bladder causing ureteric obstruction, seen between 1979 and 1989. All were under the care of one consultant urologist (J.M.T.).

## Results

All patients had G2Ta cancers. Haematuria with or without clots was the commonest symptom (89% of cases). Other symptoms were non-specific and included dysuria, hesitancy, frequency and urgency. A 21-year-old man presented with haematuria dating back several years and also nocturnal enuresis. Clinical examination was unremarkable.

Table 1 shows the X-ray findings, histopathology and treatment. Six IVUs showed varying degrees of hydronephrosis and hydroureter (Fig.), while 4 urograms showed non-functioning kidneys. The latter group of patients underwent either retrograde or antegrade contrast studies. Five IVUs also showed a filling defect in the base of the bladder.

All endoscopic examinations and treatment were carried out under general anaesthesia by one surgeon (J.M.T.). On initial examination, 2 patients had extensive tumours of the bladder and were treated by urethrocystectomy.

Case no. 4 had tumours around the ureteric orifice and in the distal ureter. After transurethral resection of the bladder tumour, she underwent nephroureterectomy.

Table 2 shows the survival in years and subsequent management. Only 5 patients were available for long-term follow-up (> 5 years).

Case no. 7 died 9 days post-operatively from pulmonary embolism (on subcutaneous heparin). Case no. 8 died 1 year after endoscopic treatment (cause unknown). Case no. 5, treated in 1981, was lost to follow-up. Two cases (nos. 9 and 10) were treated 2 years ago.

## Discussion

The present study appears to be the first to show that ureteric obstruction can be caused by superficial transitional cell cancers (Ta, T1 lesions). The standard teaching is that when urothelial cancers are associated with upper tract obstruction, it invariably means that muscle has been invaded—implying that there is a linear relationship between the depth of invasion and the incidence of obstruction (Blandy, 1982; Bailey and Love, 1984). This statement is generally true, but all patients in the

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**Table 1** Patients and Treatment

| *Initials* | *Case no.* | *Age (years)* | *Sex* | *IVU findings* | *Stage* | *Grade* | *Site* | *Treatment* |
|---|---|---|---|---|---|---|---|---|
| R.D. | 1 | 71 | M | L. Hydronephrosis | Ta | G2 | B* | Cystoscopy/TURB‡ |
| S.D. | 2 | 68 | M | L. Hydronephrosis. Filling defect l. side of bladder | Ta | G2 | B | Cystoscopy/TURB |
| L.A. | 3 | 63 | M | R. Hydronephrosis. Filling defect r. side of bladder | Ta | G2 | B | Cystoscopy/TURB |
| L.S. | 4 | 64 | F | Non-functioning r. kidney. Filling defect r. side of bladder | Ta | G2 | U†/B | Cystoscopy/TURB. R. Nephro-ureterectomy |
| J.M. | 5 | 73 | M | Non-functioning r. kidney | Ta | G2 | B | Cystoscopy/TURB |
| F.L. | 6 | 76 | M | Bilateral hydronephrosis | Ta | G2 | B | Cystoscopy/TURB |
| J.K. | 7 | 63 | M | Bilateral hydronephrosis | Ta | G2 | B | Total cystectomy and ileal conduit |
| L.D. | 8 | 72 | F | Non-functioning l. kidney. Filling defect l. side of bladder | Ta | G2 | B | Cystoscopy/TURB |
| A.M. | 9 | 21 | M | Bilateral hydronephrosis | Ta | G2 | B | Total cystectomy and ileal conduit |
| A.K. | 10 | 62 | M | Non-functioning r. kidney. Filling defect r. side of bladder | Ta | G2 | B | R. Nephro-ureterectomy. Cystoscopy/TURB |

*Bladder. †Ureter.
‡Transurethral resection of bladder tumour.

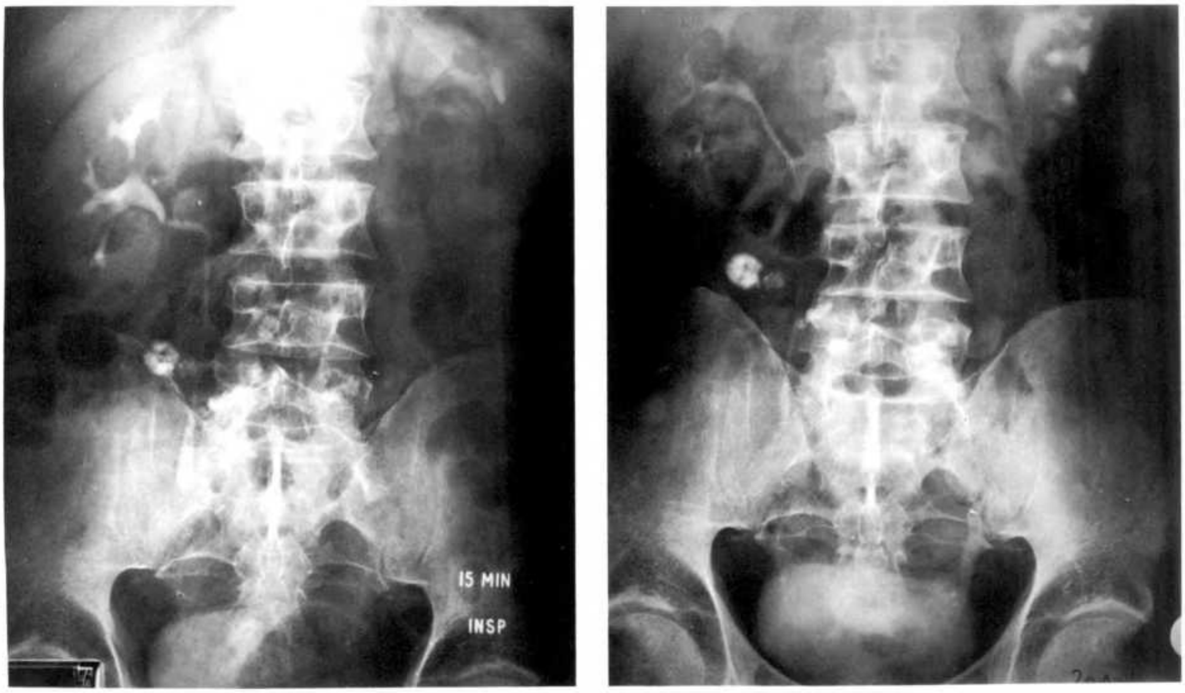

**Fig. 1** (A) Intravenous urogram showing large filling defect in left half of bladder with hydronephrosis on same side. (B) Subsequent IVU after transurethral resection of tumour confirmed relief of obstruction.

**Table 2** Survival and Subsequent Management

| *Case No.* | *Alive (years)* | *Subsequent treatment* | *Outcome* |
|---|---|---|---|
| 1 | 5½ | Cystodiathermy | Discharged |
| 2 | 5½ | TURB | Discharged |
| 3 | 5 | TURB | Discharged |
| 4 | 7½ | Cystodiathermy. Thiotepa/interferon bladder instillation | Discharged |
| 5 | 5 | TURB | Follow-up |

present series were in category Ta, showing that even the very early lesions can cause obstruction. This indicates that different mechanisms are responsible for obstruction.

In superficial lesions, it is suggested that the obstruction occurs as a result of mechanical blockage of the ureteric orifice by tumour proliferation. The combination of a narrow lumen and a tumour which tends to be proliferative would make this highly feasible. In invasive tumours, the mechanism is probably due to a combination of mechanical blockage and interference with ureteric peristalsis (due to muscle invasion).

Badenoch (1965) associated a non-functioning kidney with more malignant tumour and a poor prognosis. It would seem that all stages and grades of transitional cell carcinoma can cause upper tract obstruction, and this finding is not necessarily associated either with a poor prognosis or more aggressive treatment. Table 2 shows that these patients have a good prognosis. All responded to endoscopic treatment and none needed radical surgery. In a few cases, post-operative IVUs showed relief of obstruction. Since the results of endoscopic treatment of bladder lesions have been encouraging, there may be a place for similar treatment of the early ureteric lesions. Better pre-operative assessment is now possible with the advent of ureterorenoscopy. Direct visualisation and the availability of biopsy material can help towards more conservative treatment and also in the subsequent follow-up of these patients.

## Acknowledgement

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# Does Ethamsylate Reduce Haemorrhage in Transurethral Prostatectomy?

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Summary—A double-blind, randomised trial of 44 consecutive patients undergoing transurethral prostatectomy demonstrated that ethamsylate (Dicynene) did not reduce blood loss during either the operative or the post-operative periods.

Excessive blood loss is the most common problem in transurethral prostatectomy (TURP) and a medication that reduced haemorrhage would be very welcome.

Ethamsylate was introduced in 1959 and is used in various surgical disciplines. In urology there have been conflicting reports regarding its efficacy in TURP. Symes *et al.* (1975) reported that ethamsylate reduced blood loss during surgery and that it may reduce post-operative blood loss, but Towler and Valerio (1978) refuted both of these claims. However, in both studies the resections were quite small, a mean of only 7 g being removed by Symes *et al.* and 15.5 g by Towler and Valerio.

We therefore performed a further study in an attempt to answer the question "Does ethamsylate reduce haemorrhage in transurethral prostatectomy?"

## Patients and Methods

The study group comprised 44 consecutive patients aged 53 to 86 years (mean 72.1) admitted for TURP for bladder outlet obstruction due to clinically benign prostatic hyperplasia (BPH). Patients with a catheter *in situ* and those with clinically malignant glands were excluded. Ten patients whose glands were found to contain foci of latent carcinoma (stage TO) (UICC, 1978) were included after subsequent analysis of this subset showed no difference in blood loss.

Each patient's urine was cultured pre-operatively and full blood count, platelet count, urea, electrolytes, acid phosphatase and alkaline phosphatase levels determined.

Each patient was allocated a consecutive number and randomised by computer to receive identical-looking tablets containing either placebo or 500 mg of ethamsylate. Each patient took 1 tablet 6-hourly, starting 24 h prior to surgery and continuing until 48 h after surgery. This included 1 tablet taken with the premedication (diazepam 10 mg orally) 2 h before surgery. Surgery and the period of post-operative catheterisation were covered by oral trimethoprim.

Ten patients were operated on by the consultant surgeon and 36 by the senior registrar (Table 1).

**Table 1** Variables which could Influence Blood Loss

| | *Ethamsylate* | *Placebo* |
|---|---|---|
| No. of patients | 22 | 22 |
| Age (mean) (years) | 72.8 | 71.5 |
| Urea (mean) (mmol/l) | 6.12 | 6.85 |
| Platelet count (mean) (10/l) | 268 | 280 |
| Pre-operative urinary tract infection | 2 | 3 |
| Type of anaesthetic; relaxant | 11 | 14 |
| spinal | 9 | 4 |
| mask | 2 | 4 |
| Surgeon A | 3 | 7 |
| B | 19 | 15 |
| Mean weight of resected prostate (SD) (g) | 29.7 (16.1) | 38.2 (22.0) |

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Both used the same resection technique with an Olympus 26 or 28 F resectoscope. Following coagulation of obvious bleeding vessels at the end of resection, 40 mg frusemide were given intravenously and a 22 or 24 F simplastic 2-way catheter inserted; bladder irrigation was never used.

Three anaesthetic techniques were used (relaxant, spinal and mask), the distribution being similar between the ethamsylate and placebo groups (Table 1). Hypotensive anaesthesia was not used.

At the end of the operation the washings were placed in a container, the volume measured, the contents mixed vigorously and a sample collected in an EDTA bottle. Blood loss was determined by measuring the haemoglobin content in a Coulter counter (Hahn, 1987). Blood loss was calculated from the following equation:

$$\frac{\text{Hb concentration of sample} \times \text{volume of sample}}{\text{Hb concentration of patient's venous blood}} = \text{ml blood loss}$$

Post-operatively, all of the urine and any bladder washings were collected and treated in the same manner at 24 and 48 h.

*Statistical method*

The *t* test was used first to detect differences between the 2 treatment groups. Secondly, co-variant analysis was carried out, using the weight of the prostate resected as co-variate. Logarithmic scatter diagrams were plotted to determine the degree of variability of blood loss with increasing weights of prostate (Figs 1 and 2).

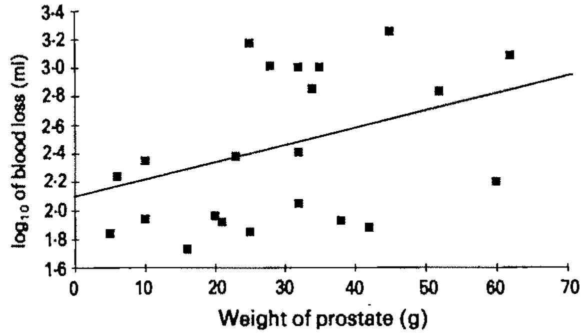

**Fig. 1** Weight of prostate resected against $\log_{10}$ operative blood loss in patients treated with ethamsylate.

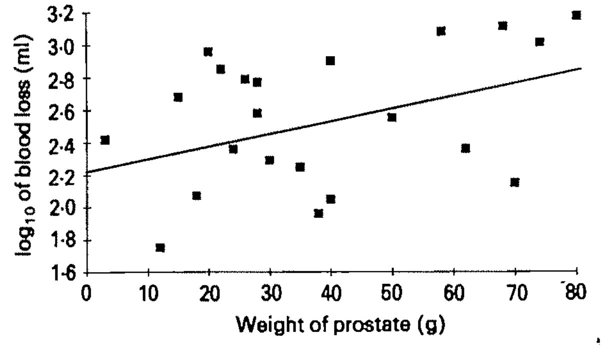

**Fig. 2** Weight of prostate resected against $\log_{10}$ post-operative blood loss in patients receiving placebo.

## Results

The code was broken after 40 cases by Delandale Laboratories, who performed a preliminary analysis and declared that no further cases were required for a definite result. Four further patients had been treated, bringing the total to 44.

The variables which could influence blood loss in the two groups are shown in Table 1. The significant variables were evenly distributed. The mean blood loss for surgeon A was 547 ml and of surgeon B 513 ml. The distribution of blood losses is shown in Figure 3 (operative loss) and Figure 4 (post-operative loss).

Of the 10 patients with TO carcinoma, 3 received ethamsylate and 7 had placebo. Their resection weights were a mean of 27.1 g compared with 36.1 g for the 34 patients with BPH. Their blood losses were similar to those of the patients with BPH (Table 2) and showed no response to ethamsylate. The results of both groups were therefore amalgamated.

No complications were noted due to ethamsylate and there were no deaths during the study period; 2 units of blood were given to 2 patients receiving ethamsylate and 2 receiving placebo. The mean post-operative stay in hospital was 5.0 days in the ethamsylate group and 4.9 days in the placebo group.

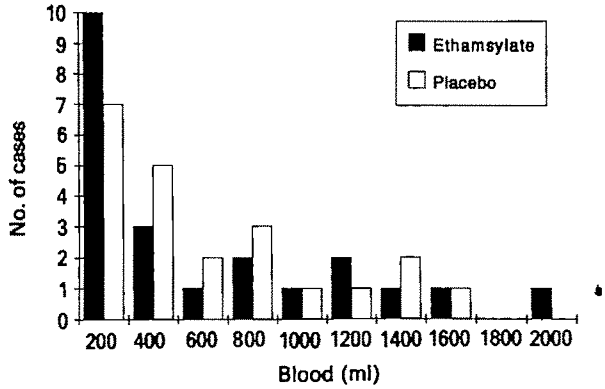

**Fig. 3** Operative blood loss in patients receiving ethamsylate and those receiving placebo.

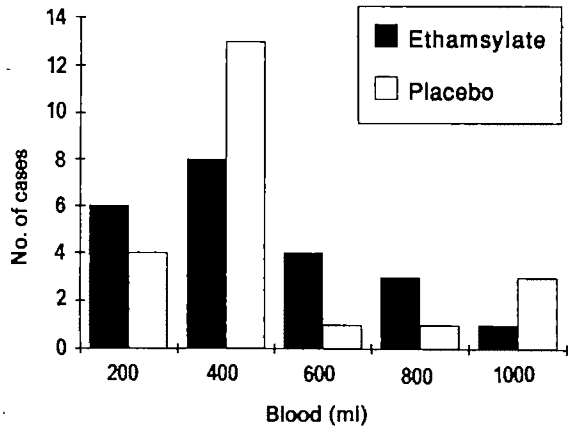

**Fig. 4** Post-operative blood loss in patients receiving ethamsylate and those receiving placebo.

*Statistical analysis*

The difference in blood loss between the 2 groups was very small. To exclude the known relationship between blood loss and weight of prostate resected, co-variant analysis was performed, starting with the $t$ test.

**Table 2** Mean Operative and Post-operative Blood Loss

| | *Ethamsylate (ml)* | *Placebo (ml)* |
|---|---|---|
| 10 patients with carcinoma | | |
| Operative | 463 | 407 |
| Post-operative | 374 | 333 |
| 32 patients with BPH | | |
| Operative | 527 | 581 |
| Post-operative | 381 | 386 |
| All patients | | |
| Operative (SD) | 515 (547) | 525 (442) |
| Post-operative (SD) | 377 (212) | 373 (235) |

For weight, $t = 1.47$ (difference in mean weights divided by standard error of difference). Based on the degrees of freedom 42 (44–2), the value of $t$ was not significant (*i.e.* $P > 0.05$). For operative blood loss $t = 0.066$ and for post-operative blood loss $t = 0.098$, neither of which was significant.

Analysis of co-variance of the data using the resected weight as the co-variate was performed. The conclusion was that the regression of the operative weight was significant for ethamsylate ($r = 0.37, P = < 0.1$) and placebo ($r = 0.48, P < 0.05$). The slopes did not differ significantly and the mean blood loss was 11.2 ml/g prostate resected. The displacement between the 2 regressions was not significant, indicating that after allowing for the known effect of operative weight on blood loss, the effect of ethamsylate was not significant.

In summary, ethamsylate was found to have no effect on blood loss.

Regarding the relationship between the weight of the prostate gland resected and the operative and post-operative blood loss, the above positive correlation was found. The resection weights were approximately symmetrically distributed but the blood losses were positively skew. However, when expressed as log 10, there was nearly uniform residual variance at increasing weights. This is shown in Figures 1 and 2 in which log (blood loss) is used as the independent variable. Nevertheless, the ethamsylate and placebo groups still showed no significant difference in blood loss.

## Discussion

The actions of ethamsylate are described as decreased capillary fragility, increased platelet adhesiveness and increased rate of release of intrinsic thromboplastin. These 3 factors work together to

**Table 3** Results of Studies on the Effect of Ethamsylate in TURP

| | *Resected weight of prostate (g)* | | *Operative blood loss (ml)* | | *Post-operative blood loss (ml)* | |
|---|---|---|---|---|---|---|
| | *Ethamsylate* | *Placebo* | *Ethamsylate* | *Placebo* | *Ethamsylate* | *Placebo* |
| Symes *et al.* (1975) (76 cases) | 9 | 5 | 17 | 72 | 38 | 103 |
| Towler and Valerio (1978) (94 cases) | 13 | 18 | 326 | 273 | 803 | 618 |
| Munson (personal communication) (107 cases) | 24 | 16 | 197 | 167 | 258 | 200 |
| Lyth and Booth (present series) (44 cases) | 30 | 38 | 515 | 525 | 377 | 373 |

reduce the bleeding time (Harrison and Campbell, 1976).

The 2 previous studies on ethamsylate in TURP have come to different conclusions. There were differences in the trials, such as type of anaesthesia, but the figures in Table 3 suggest why different conclusions were reached. The study by Symes *et al.* (1975), showing apparent benefit from ethamsylate, involved very small blood losses from extremely small resections. This concurs with the mode of action of ethamsylate, which is at a capillary level.

A further unpublished study at King's College Hospital (Munson, personal communication) involved 107 patients with a mean resected weight of 20 g. Apart from a small reduction in post-operative blood loss, no overall benefit was found, which also supports our findings.

Although ethamsylate may be of benefit in other surgical specialties or other urological situations (*e.g.* haemorrhage due to radiation cystitis), it was concluded that it has no role in the reduction of blood loss in transurethral prostatectomy.

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# Prostate Tumour Markers and Differentiation Grade in Prostatic Cancer

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Summary—Serum acid phosphatase activity, prostate specific phosphatase and prostate specific antigen were measured in 100 patients with prostatic cancer. The patients were divided according to the differentiation grade into 3 groups: G1 (well), G2 (moderately) and G3 (poorly differentiated) carcinoma. Bone metastases were identified by scintigraphy. Among the 76 M0 patients the mean levels of all 3 markers were slightly higher in patients with moderately differentiated prostatic carcinoma. Among the 24 M1 patients the primary tumour was either G2 (18 patients) or G3 (6 patients); none had G1 lesions. Significantly higher serum ACP and PAP levels were found in patients with G2 tumours than in those with G3 lesions. It was concluded that the histological differentiation grade of prostatic carcinoma did affect serum levels of prostatic tumour markers; the tendency towards higher levels in the G2 group was noticeable in both non-metastatic and metastatic cases despite the limited number of patients in the latter category. In clinical practice this information may be an important additional tool in staging prostatic cancer.

Determination of prostatic tumour markers is an important aid in clinical practice for the staging and monitoring of prostatic cancer patients. Markers are known to be elevated in a majority of patients with metastatic disease (Gutman and Gutman, 1938; Ahmann and Schifman, 1987; Romas, 1987). Conflicting results have been reported on the possible relationship between serum tumour marker levels and the differentiation grade of the primary tumour (Bates *et al.*, 1982; Stamey and Kabalin, 1989).

We have investigated whether there is any correlation between the serum levels of acid phosphatase activity (ACP), prostate specific acid phosphatase (PAP), prostate specific antigen (PSA) and the differentiation grade of prostatic carcinoma.

## Patients and Methods

The study group comprised 100 patients, aged 53 to 91 years (mean 70.0), with histologically verified prostatic cancer. The malignancy was graded according to the World Health Organization (1980) International Classification of Tumours (G classification). The stage of the tumour was determined according to the UICC (1987) classification. The M0 category was subdivided into intracapsular (T1-2) and extracapsular (T3–4) groups. Transrectal ultrasonography was performed in all patients to determine more accurately the local stage. Total prostatectomy was performed in 16 cases.

Bone metastases were identified by scintigraphy, using a large field of view gamma camera equipped with whole body imaging devices. Each patient was imaged 3 h after an intravenous dose of approximately 600 MBq of $^{99m}$ TC-labelled dicarboxypropane diphosphate (Hoechst, FRG). The distribution of patients into TM and G categories is presented in Table 1.

Serum samples for the assay of tumour markers were collected before treatment. The samples were stored at $-20°C$ until assayed, all assays being carried out in duplicate. Serum acid phosphatase activity was measured using p-nitrophenyl-phosphate as substrate (Bessey *et al.*, 1946). For radioimmunoassay of serum prostatic acid phosphatase the method of Vihko *et al.* (1980, 1981) was

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**Table 1** Distribution of Prostatic Cancer Patients into TM and G Categories

| | *Histological differentiation grade* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *TM category* | *G1* | *(%)* | *G2* | *(%)* | *G3* | *(%)* | *Total* | *(%)* |
| T1-2 M0 | 22 | (60) | 12 | (32) | 3 | (8) | 37 | (100) |
| T3-4 M0 | 10 | (26) | 19 | (48) | 10 | (26) | 39 | (100) |
| T1-4 M1 | 0 | (0) | 18 | (75) | 6 | (25) | 24 | (100) |
| Total | 32 | | 49 | | 19 | | 100 | |

used. Serum prostate specific antigen was determined by an immunoradiometric assay, using reagents from Hybritech Inc. (San Diego, USA).

The significance of differences in the mean levels of serum tumour markers, after logarithmic transformation of the results, was assessed by Student's *t* test. The analysis of variance was applied when appropriate.

## Results

The mean serum tumour marker values and standard deviations are presented in Table 2. The distribution of serum ACP, PAP and PSA levels into various G categories among M0 patients is shown in Figure 1. In patients with moderately differentiated prostatic cancer (G2), the mean serum levels of all 3 tumour markers were higher than in patients with well (G1) or poorly (G3) differentiated disease. The differences between the categories were not, however, statistically significant ($P<0.05$).

In the M1 patients the mean ACP and PAP levels were statistically significantly higher ($P=0.03$ and $P=0.01$ respectively) in the G2 than in the G3 category. There were no significant differences ($P=0.10$) between the mean serum PSA levels in G2 and G3 patients. The distribution of the corresponding serum ACP, PAP and PSA levels into various G categories among M1 patients is presented in Figure 2.

**Table 2** Mean Serum Levels (±2 SD) of Prostate Tumour Markers (ACP, PAP and PSA) in G Categories in M0 and M1 Patients

| | *M0* | | | *M1* | |
|---|---|---|---|---|---|
| | *G1* | *G2* | *G3* | *G2* | *G3* |
| ACP | | | | | |
| Mean | 8.8 | 10.2 | 79 | 58.4* | 21.8 |
| +2 SD | 17.2 | 43.2 | 16.6 | 2203.9 | 85.2 |
| −2 SD | 4.5 | 2.4 | 3.7 | 1.5 | 5.6 |
| No. | 24 | 24 | 12 | 17 | 6 |
| PAP | | | | | |
| Mean | 2.8 | 3.8 | 2.3 | 72.2† | 15.1 |
| +2 SD | 16.1 | 47.9 | 12.8 | 5161.6 | 159.6 |
| −2 SD | 0.4 | 0.3 | 0.4 | 1.0 | 1.4 |
| No. | 32 | 31 | 13 | 18 | 6 |
| PSA | | | | | |
| Mean | 14.4 | 32.5 | 13.0 | 415.7‡ | 111.9 |
| +2 SD | 260.1 | 1534.6 | 137.7 | 16155.2 | 9509.1 |
| −2 SD | 0.8 | 0.7 | 1.2 | 10.7 | 1.3 |
| No. | 32 | 31 | 13 | 18 | 6 |

| Significance: | ACP | PAP | PSA |
|---|---|---|---|
| M1G2 vs M1G3 | $P=0.03$* | $P=0.01$† | $P=0.10$‡ |

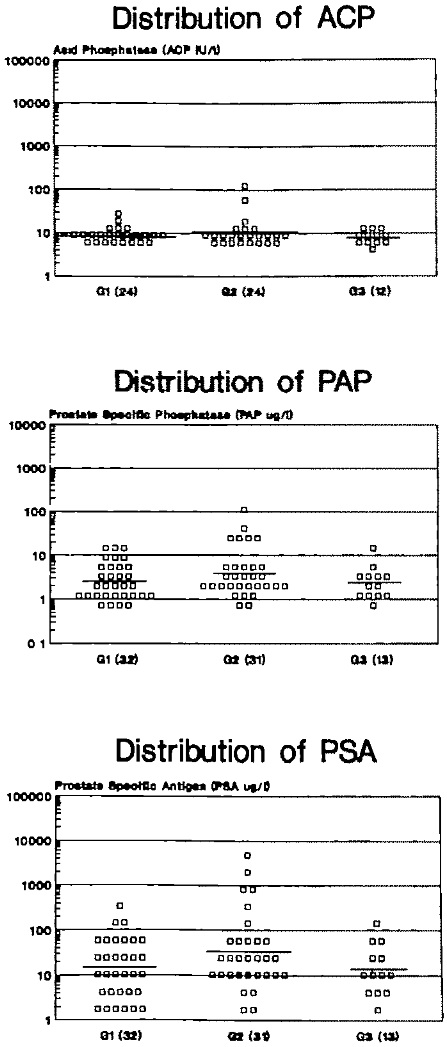

**Fig. 1** Distribution and mean serum values (—) of prostate tumour markers (ACP, PAP and PSA) in M0 prostatic carcinoma patients according to histological differentiation grade.

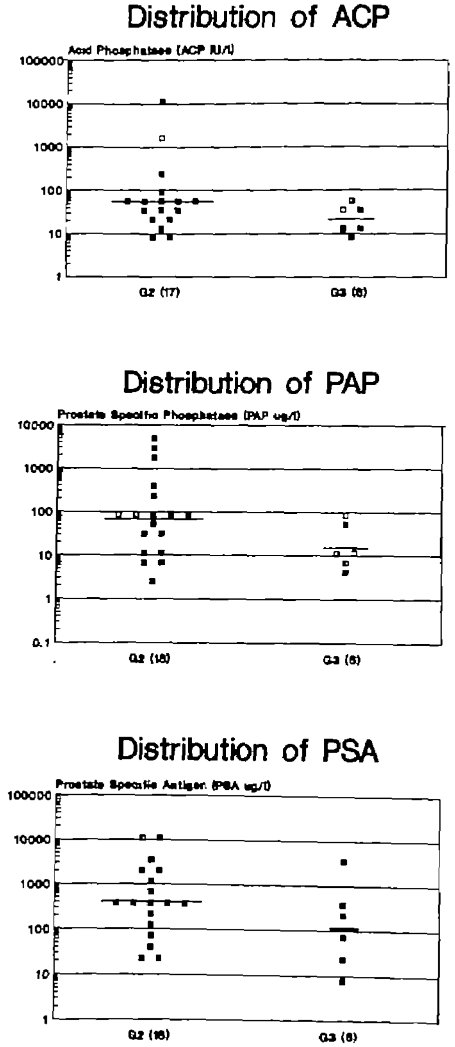

**Fig. 2** Distribution and mean serum values (—) of prostate tumour markers (ACP, PAP and PSA) in M1 prostatic carcinoma patients according to histological differentiation grade.

## Discussion

A correlation between prostate tumour markers and advancing clinical stage has been well documented in recent years (Oesterling *et al.*, 1987; Stamey *et al.* 1987; Stamey and Kabalin, 1989; Haapiainen *et al.*, 1990). The volume of primary tumour and/or its metastases may not be the only factor correlating with tumour marker levels; the ability of different malignant cells to produce them may also vary. In the study by Stamey and Kabalin (1989), serum prostate specific antigen correlated proportionally with increasing Gleason score. It has been verified immunohistochemically that in carcinoma of the prostate there is a correlation between prostate specific acid phosphatase staining, the degree of differentiation and the ability of the tumour to form a gland: staining was more intense and uniform in well differentiated tumours and less intense and more variable in poorly differentiated tumours (Bates *et al.*, 1982).

In the present study, the patients were divided into 3 groups according to the differentation grade of the primary tumour. In both M0 and M1 patients the serum ACP, PAP and PSA levels were higher in the G2 patients. Oosterom *et al.* (1986) noted a correlation between differentiation grade and PAP levels in M0 patients; higher PAP values were observed in patients with undifferentiated tumours, but no correlation was found within the group of patients with metastases. Griffiths (1982) suggested, however, that patients with a more dedifferentiated type of tumour had lower serum PAP values. This is in agreement with our results and with other biochemical and immunochemical studies (Downey *et al.*, 1954; Woodward, 1956; Foti *et al.*, 1977; Bates *et al.*, 1982).

We tried to eliminate the effect of advancing stage on serum tumour marker levels by examining the distribution separately in the M0 and M1 categories. In the non-metastatic group, 42% of the patients were G1, whereas there were no well differentiated tumours among M1 patients. G3 tumours accounted for 17% in the M0 category and 25% in the M1 category. This correlation between differentiation grade and presence of metastases has been reported previously (Barzell *et al.*, 1977).

The most interesting finding in our study was the presence of higher tumour marker levels in patients with G2 tumours than in those with G1 or G3 tumours. The difference between G1 and G2 may be due to the fact that G1 tumours had a smaller tumour mass and therefore lower tumour marker levels. The fact that G3 was associated with lower serum tumour marker levels than G2 may be explained by the fact that the expression of prostate tumour markers is reduced or lost with advancing anaplastic changes in the tumour. This could explain the clinical observation that some patients with very advanced prostatic cancer have normal tumour marker levels.

When evaluating tumour marker levels it seems advisable to take into consideration the histological differentiation grade of prostatic carcinoma. The markers seem less useful in patients with poorly differentiated prostatic cancer. The knowledge of this relationship between serum tumour marker level and differentiation grade may be of importance when tumour markers are used as an aid in the staging of prostatic cancer.

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# Treatment of Benign Prostatic Hyperplasia with Phytosterols

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Summary—In a randomised, double-blind study, the preparation Curbicin, obtained from pumpkin seeds and dwarf palm plants (*Cucurbita pepo L.* and *Sabal serrulata*), was compared with a placebo in the treatment of symptoms caused by prostatic hyperplasia; 53 patients took part in the study, which was carried out over a 3-month period. Urinary flow, micturition time, residual urine, frequency of micturition and a subjective assessment of the effect of treatment were all significantly improved in the treatment group. No untoward side effects were noted.

For many years, particularly in Europe, extracts from pumpkin seeds (*Cucurbita pepo L.*) and the fruits of dwarf palms (*Sabal serrulata*) have been used in folk medicine as a remedy for micturition problems caused by the prostate (Madaus, 1979). During the past few years, clinical studies carried out under medical supervision with these preparations have shown them to be beneficial (Mandressi *et al.*, 1987; Pannunzio *et al.*, 1987; Carbin and Eliasson, 1989).

The exact mechanism of action of Curbicin is not clear, but it has been shown to decrease the binding capacity of androgen receptors to testosterone (Andersson *et al.*, 1977; Schmidt, 1984), while in some studies *Sabal* extract has been shown to have an inhibitory effect on 5α-reductase (Carilla *et al.*, 1984; Sultan *et al.*, 1984; Pannunzio *et al.*, 1987). Thus Curbicin appears to have a dual action in influencing the development of prostatic hyperplasia. The competitive binding of phytosterols to androgen receptors could be explained by the similarity of their chemical structure to androgens and oestrogens (Ourisson *et al.*, 1964; Schöpflin *et al.*, 1966).

In a double-blind pilot study in 26 patients it was shown that a preparation with extracts of both *Cucurbita pepo L.* and *Sabal serrulata* (Curbicin) significantly decreased nocturia, but other variables, (*e.g.* residual urine, urinary flow rate and frequency of diurnal voiding) were not significantly different between the 2 groups (Carbin and Eliasson, 1989). However, the sample studied was small and randomisation was not stratified. The study reported here was carried out in a larger group of patients with early symptoms of outflow obstruction due to benign prostatic hyperplasia.

## Patients and Methods

A double-blind, placebo-controlled study was carried out in conjunction with 6 general practitioners (4 in Sweden and 2 in Denmark) to assess the value of Curbicin in the treatment of patients with voiding problems due to BPH.

The criteria for the inclusion of patients in the study, after having obtained informed consent, were as follows: males between the ages of 50 and 80 years with symptoms of at least 3 months' duration; the presence of benign prostatic hyperplasia on the basis of a history, clinical examination of the prostate and acid phosphatase determination; patients not previously treated with Curbicin. Patients in imminent need of surgery because of the severity of symptoms or residual urine > 300 ml were excluded from the study.

The series included 55 patients. Curbicin contains 160 mg of standardised extract PS6 from *Cucurbita pepo L.* seeds (80 mg) and *Sabal serrulata* fruits (80 mg). The 2 extracts are separately stan-

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dardised with respect to a batchwise controlled total content of specific phytosterols.

The placebo tablets were identical in smell, consistency, shape, colour and taste to the active compound. The tablets were swallowed whole in a dose of 2 tablets 3 times a day. The duration of treatment was 3 months.

The patients were randomly allocated to receive either active compound or placebo according to a centrally controlled code list. At the conclusion of the study 26 patients had received active therapy and 27 placebo, the 2 groups being stratified.

The subjective variables studied were (1) difficulties with voiding, (2) frequency of urination during the day, (3) nocturia. The subjective symptoms were assessed as follows: much better, better, the same, worse.

The objective parameters were (1) urinary flow rate measured in ml/s, (2) voiding time measured in seconds, (3) residual volume. In most patients this was determined by catheterisation, but in 9 cases (5 in the active treatment group and 4 in the placebo group) residual urine was determined by ultrasound. For each individual patient the same method was used both before and after treatment.

The subjective variables were tested for significance with the Mann Whitney U test and the objective variables with Student's $t$ test, first through pairwise comparisons before and after treatment within each group. Thereafter an intergroup comparison of the respective mean differences was done. Non-parametric tests gave the same result as the $t$ test.

## Results

Of the 55 patients entered into the study, 2 were withdrawn: 1 because of alcoholism and the other because of acute urinary retention requiring operative treatment. The results of the randomisation of patients is shown in Table 1. The 2 groups were evenly matched, with no significant differences in the variables ($P < 0.1$).

The results of the subjective and objective parameters studied showed a statistically significant improvement in patients treated with Curbicin and no change in those receiving placebo (Table 2).

No untoward side effects were reported.

## Discussion

The results of this study showed a significant subjective and objective improvement in patients treated with Curbicin. The difference between these results and those of the earlier pilot study (Carbin and Eliasson, 1989), where improvement was found in only 1 variable, nocturia, may be explained by poor stratification between the groups and by the fact that in the present study the preparation contained an increased amount of extract from *Sabal serrulata* (80 instead of 15 mg). There was also a refinement of the extraction process for *Sabal serrulata*.

These findings compare favourably with those of earlier reports on the use of extracts from dwarf palms (Mandressi *et al.*, 1987). The treatment of pronounced symptoms of prostatic outflow tract obstruction is undoubtedly surgical. However, milder symptoms may be present for a considerable period of time while the patient is awaiting surgery. A small minority of patients are unfit for surgery because of coexisting disease. In both of these situations there is need for effective medical treatment to alleviate symptoms. Further long-term studies with Curbicin will indicate the benefits of this compound in the treatment of patients with mild symptoms of outflow tract obstruction due to prostatic hyperplasia.

**Table 1** Results of randomisation

| | *Curbicin (n=26)* | | | *Placebo (n=27)* | | |
|---|---|---|---|---|---|---|
| | *Mean* | *Range* | *SD* | *Mean* | *Range* | *SD* |
| Age (years) | 62.0 | 52–72 | ±6.7 | 61.2 | 51–72 | ±5.8 |
| Flow (ml/s) | 6.8 | 4.2–9.8 | ±1.4 | 6.6 | 4.1–9.2 | ±1.3 |
| Micturition time (s) | 16.2 | 12.2–20.7 | ±1.7 | 15.6 | 12.2–22.0 | ±2.4 |
| Residual volume (ml) | 135 | 55–225 | ±44 | 128 | 75–220 | ±39 |
| Diurnal frequency | 7.3 | 5–9 | ±1.3 | 7.8 | 5.5–10 | ±1.1 |
| Nocturnal frequency | 1.9 | 0.5–4 | ±0.6 | 2.1 | 1.5–3 | ±0.6 |
| Duration of illness (years) | 3.0 | 1–7 | ±1.8 | 3.2 | 1–8 | ±1.9 |

**Table 2** Effect of Treatment on the Variables (means and standard deviations)

| | *Preparation* | *Mean value before treatment* | *Mean value after 3 months* | *Difference between mean values* | *P value within the groups* | |
|---|---|---|---|---|---|---|
| Urinary flow (ml/s) | Curbicin | 6.7±1.4 | 9.7±3.6 | +3.0±4.0 | <0.001 | <0.001 |
| | Placebo | 6.6±1.3 | 6.9±1.8 | +0.3±1.7 | NS | |
| Micturition time (s) | Curbicin | 16.2±1.7 | 13.8±2.8 | −2.4±3.6 | <0.01 | <0.05 |
| | Placebo | 15.6±2.4 | 14.9±1.9 | −0.7±2.9 | NS | |
| Residual volume (ml) | Curbicin | 135.0±43.9 | 92.5±48 | −42.5±62.1 | <0.01 | <0.01 |
| | Placebo | 127.6±39.0 | 120.0±37.5 | −7.6±22.9 | NS | |
| Diurnal frequency | Curbicin | 7.3±1.3 | 6.3±1.0 | −1.0±1.5 | <0.05 | <0.05 |
| | Placebo | 7.8±1.1 | 7.9±0.8 | +0.1±0.8 | NS | |
| Nocturnal frequency | Curbicin | 1.9±0.6 | 1.4±0.7 | −0.6±0.7 | <0.01 | <0.01 |
| | Placebo | 2.1±0.7 | 2.0±0.9 | −0.1±0.6 | NS | |

| *Subjective variables* | *Preparation* | *Much better* | *Better* | *The same* | *Worse* | *P value between groups* |
|---|---|---|---|---|---|---|
| Dysuria | Curbicin | 10 | 11 | 4 | 1 | <0.001 |
| | Placebo | 1 | 4 | 14 | 8 | |
| Patient's evaluation of therapy | Curbicin | 6 | 16 | 3 | 1 | <0.001 |
| | Placebo | 0 | 3 | 19 | 5 | |

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# Acute Epididymitis: Why Patient and Consort must be Investigated

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Summary—In this prospective study of 49 patients under 35 years of age with clinically diagnosed epididymitis, detailed microbiological investigation identified an infective cause in 67%. *Chlamydia trachomatis* was the commonest agent, present in 25 patients, but in 12 of these detection was based solely on raised antibody titres; 20 of the 28 female consorts screened were partners of men with chlamydial epididymitis and 80% of them were also positive for this infection. Isolating the micro-organism from 14 of 16 consorts indicated active infection despite the negative swabs from the men. If this important infection is to be adequately treated we recommend that all patients in this age group with epididymitis and their partners should be referred to a specialist unit with access to full chlamydia laboratory facilities.

Patients who develop epididymitis present to a variety of clinicians: by self-referral to general practitioners, to genitourinary physicians, to accident and emergency units, or as secondary referrals to general surgeons and urologists. Awareness that this condition is caused by infections, which in younger men are frequently sexually transmissible, has become more widespread but few of these clinicians have access to a full range of microbiological laboratory facilities, especially when patients present outside the normal working day. Pressure to start treatment often results in antibiotic therapy being instituted before the patient has been investigated. This approach can enable the clinician to avoid facing the difficult situation which a sexually transmissible disease creates, especially when the patient is an apparently happily married man. The response to treatment is not a reliable indicator that the correct one has been chosen, since the natural history of this condition, which was established during the period when simple bed rest was advocated, is of gradual resolution in most cases. Whilst it remains unclear how damaging such untreated infections are to the functional integrity of the epididymis, it is all too clear what they can do to fallopian tubes and thus the fertility of the female partner (Oriel and Ridgway, 1982a).

*Chlamydia trachomatis* has now been established as the commonest cause of epididymitis in young men, both in the USA and in this country (Grant *et al.*, 1987). Diagnosis is made by isolation of *C. trachomatis* and or serological testing, but full laboratory facilities are not available in all hospitals. The Frei test, which was initially used to diagnose lympho-granuloma venereum (LGV), another chlamydial infection, lost its place in clinical practice because of the incidence of apparently false positive results. We wondered to what extent these results may have reflected patients with other manifestations of chlamydial infection.

We therefore studied patients with epididymitis and their consorts to assess the need for microbiological investigation and we also undertook a preliminary study of a modified Frei test using purified inoculum.

## Patients and Methods

From October 1987 to December 1988, 49 patients aged 35 years or less who presented with epididym-

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989 itis at the Departments of Urology, Accident and Emergency and Genitourinary Medicine were studied. In 44 patients a clinical diagnosis was made when a tender swollen epididymis was found and in 5 patients epididymitis was found at surgical exploration which had been undertaken to exclude testicular torsion. A genitourinary history was taken followed by genital examination. Investigations are listed in Table 1.

Urethral swabs were Gram stained and the culture techniques used were sufficient for the isolation of *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *Ureaplasma urealyticum* and anaerobes.

*Chlamydia isolation.* In 26 patients culture was performed in McCoy cell lines using the modified technique of Ripa and Mardh (1977). In 23 patients the chlamydia antigen detection (Chlamdiazyme) technique was used.

*Chlamydia serology.* Measurement of IgG chlamydia antibody titres was by the ELISA assay (Levy *et al.*, 1983) in 26 patients and by single serotype immunofluorescence (Thomas *et al.*, 1976) in 23 patients.

*Semen.* 10 patients produced a semen sample for bacterial culture and chlamydia isolation.

*Modified Frei test.* The inoculum was prepared from McCoy cell cultures inoculated with the L2 strain of *C. trachomatis*, whilst the control was from an uninfected cell suspension; 22 patients were skin tested by injecting 0.1 ml of the test inoculum and 0.1 ml of the control solution intradermally into separate sites on the forearm; the result was read 24 to 48 h later and assessed by the presence or absence of erythema, its diameter and the presence or absence of induration. An erythematous reaction of 5 mm or more was regarded as a positive result.

*Female consorts.* In all, 28 consorts of 26 patients were traced and investigated. The following specimens were obtained: (1) cervical and urethral swabs for chlamydia antigen detection (Chlamdiazyme) and gonococcal culture; (2) vaginal swab for microscopy and bacterial culture; (3) venous blood for chlamydia serology (IgG single serotype microimmunofluorescence).

## Results

A history of urethral discharge was elicited in only 10 of 49 patients (20%); 6 patients (12%) had experienced a previous episode of urethritis. However, objective evidence of urethritis, which was diagnosed when there were more than 5 polymorphonuclear leucocytes per high powered field, was found in 22 of 49 patients (67%). Epididymitis was bilateral in only 2 patients.

An infective agent was identified in 33 of 49 patients (67%). *C. trachomatis* was the commonest agent identified. It was isolated from 13 patients and in a further 12 patients the antibody titre was 1 in 512 or greater. Thus there was evidence of this infection in 51% of patients. Other organisms were isolated from 4 of these patients, as shown in Table 2, which also identifies the agents found in patients without chlamydial infection.

The study group included 38 single patients; 4 married men and 2 divorcees had chlamydial epididymitis and the remaining 4 married men had non-chlamydial epididymitis.

*Modified Frei Test.* Of 10 patients with chlamydial epididymitis, 9 developed positive skin tests. The tests were negative in all 12 patients in whom no *C. trachomatis* was isolated and their antibody titres were less than 1 in 512.

*Female Consorts.* Of 28 women, 15 (54%) were asymptomatic. Ten women had a symptomatic vaginal discharge, 2 had experienced mild abdominal pain and 1 admitted to dyspareunia; 20 of the 28 women were partners of men with chlamydial epididymitis and 16 of the 20 consorts (80%) also

**Table 1** Investigations

| | *Microscopy* | *pH* | *Bacterial culture* | *Chlamydia isolation* | *Serology* |
|---|---|---|---|---|---|
| Urethral swab (UR) | x | | x | x | |
| First void urine (VB1) | x | | x | | |
| Mid-stream urine (VB2) | x | | x | | |
| Prostatic fluid (EPS) | x | x | x | | |
| Post-massage urine (VB3) | x | | x | | |
| Semen | | | x | x | |
| Venous blood | | | | | x |

**Table 2** Organisms other than *C. trachomatis* and Site of Isolation

| *CT isolate positive* | *CT serology positive* | *CT negative* |
|---|---|---|
| *E. coli*: VB1+2 semen<br>*B. fragilis*: EPS | *N. gonorrhoeae*: UR, semen<br>*Str. agalactiae*: UR VB2+3, semen | *N. gonorrhoeae*: UR<br>*E. coli*: VB2<br>*E. coli*: UR, EPS, VB1+2+3<br>*U. urealyticum*: UR, EPS<br>*U. urealyticum*, *G. vaginalis* and mixed anaerobes: EPS<br>*G. vaginalis*: UR, EPS, semen<br>*G. vaginalis*: UR, VB1+2<br>*G. vaginalis* and mixed anaerobes: UR+EPS |

had evidence of chlamydial infection (chlamydia isolation, 14; chlamydia antibody titre >1 in 512, 2). Other organisms were isolated from 12 of the 16 chlamydia-positive consorts: *N. gonorrhoeae* (2); *Gardnerella vaginalis* (8); *Trichomonas vaginalis* (1); *M. hominis* (4); *U. urealyticum* (2); anaerobes (2). The organisms isolated from 3 of 8 women who were consorts of men with non-chlamydial epididymitis were *C. trachomatis* (1), candida (1). *G. vaginalis* (1).

## Discussion

The appearance of a painful scrotal swelling causes the patient great anxiety as to its nature in addition to the considerable discomfort he experiences. Physical examination may suggest the diagnosis of epididymitis but it can be very difficult to distinguish this from testicular tumours. Identifying an active lower genitourinary infection provides strong supportive evidence of the diagnosis. Studies undertaken in the USA have shown a very good correlation between the organisms isolated from epididymal aspirates and those producing active urethritis, urinary infection or prostatitis (Berger *et al.*, 1980). Epididymal aspiration cannot be advocated for routine use as it may damage the delicate tubular structure but the examination of fractional urines, urethral swabs and expressed prostatic secretion will be performed routinely in units which have a special interest in lower urinary tract infections in men.

Our finding that in young men sexually transmissible infections, in particular *C. trachomatis*, are found in the majority of patients with epididymitis supports other observations. These contrast with the report by Pearson *et al.* (1988) of an incidence of chlamydial infection of only 30%; 7 of their 27 patients presented at intervals after vasectomy with symptoms which may have had a different pathogenesis from that of true epididymitis. Whilst we found evidence of prevailing chlamydial infection, surprisingly few patients gave a history of a urethral discharge. Lack of symptoms is often a feature of the female consort, in whom there is also a very high incidence of active chlamydial infection. The potentially damaging effect of this infection on the fallopian tubes is well recognised and must represent a cause of infertility which one should make every effort to prevent. Antibiotic therapy with erythromycin or tetracycline is effective in eradicating this infection, but treatment may need to be prolonged. Two weeks is the minimum length recommended (Oriel and Ridgway, 1982b), but experience of treating prostatitis has led some clinicians to treat patients with epididymitis for 6 weeks (Grant *et al.*, 1985). Adequate follow-up is also essential in order to ensure that the infection has been eradicated, especially as epididymitis will in many cases eventually resolve without specific treatment. It remains difficult to assess the effect of epididymitis on future fertility, particularly as this condition is usually unilateral, but prompt treatment with appropriate antibiotics must offer the most effective way of reducing late sequelae.

Controversy still surrounds the use of serological tests in the diagnosis of chlamydial infections (Treharne and Forsey, 1983). Isolating an obligatory intracellular organism requires more careful swabbing than for bacterial infection. Endourethral swabs identify a higher incidence of chlamydial infection than meatal swabs. In nearly half of the patients in this study the micro-organism was not isolated but high antibody titres were found. This might reflect inadequate swabbing techniques or the fact that active infection is no longer present in the urethra, but the latter is not supported by the high incidence of positive isolates from their consorts. This finding alone indicates the benefit gained from carefully screening all partners of patients with epididymitis and contrasts with the recommendation of Pearson *et al.* (1988) that only the consorts of patients from whom an infection is isolated need to be examined. These observations are particularly important for clinicians who do not have access to a chlamydia serology service.

The preliminary results of our evaluation of the modified Frei test are encouraging. This might prove to be a useful adjunct in diagnosis, especially as it is simple to perform and does not require laboratory facilities. It clearly merits further evaluation.

Although *C. trachomatis* was the most common infective agent identified in both patients and consorts, other organisms were found. *Escherichia coli* and *N. gonorrhoeae* are recognised as aetiological agents in epididymitis (Harnish *et al.*, 1977) and require specific antibiotic therapy. However, the role of *U. urealyticum*, *G. vaginalis* and anaerobes remains unclear, although there is some evidence to implicate *U. urealyticum* and *Bacteroides urealyticum* in the pathogenesis of non-gonococcal urethritis (Paavonen *et al.*, 1978; Taylor *et al.*, 1986). These organisms might not be isolated routinely in a laboratory and indicate another area where more research is required. We were impressed by the dramatic response of 2 patients when appropriate metronidazole therapy was instituted. Semen samples did not add anything to the microbiological data available from fractional urines, urethral swabs and expressed prostatic secretion.

Epididymitis is a condition which can cause young men a great deal of anxiety. Early referral to a unit which can exclude a testicular tumour or torsion and establish a positive diagnosis is to be recommended. A full explanation of the nature of the condition and the need for detailed investigation of both patient and partner is accepted when the patient realises that this is a condition which is eminently treatable if appropriate therapy is given.

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# Semen Analysis in Patients Operated on for Impalpable Testes

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Summary—Semen analysis was performed on 48 men who had undergone orchiopexy, 40 for unilateral impalpable testes and 8 for bilateral impalpable testes. Patients with unilateral impalpable testes had varying sperm analysis; 18 (86%) of the 23 patients with unilateral impalpable canalicular testes had normal sperm analysis. All patients with bilateral impalpable testes were azoospermic. The subsequent quality of the semen is dependent upon the original anatomical positions of the undescended testes.

There is controversy as to the fertility status of patients with cryptorchidism. The whole subject of undescended testes is beset by many problems but the question of whether or not a testis is retractile or truly undescended is a central issue. Recently we reported the results of semen analysis in 142 men who had undergone orchiopexy for cryptorchidism. The fertility potential in these patients was related to the original position of the testes; most men with unilateral cryptorchidism or bilateral undescended testes in the superficial inguinal pouch produced normal or acceptable semen (Puri and O'Donnell, 1988). In the present study we present data on semen analysis in patients operated on for clinically impalpable testes.

## Patients and Methods

Between 1957 and 1975, 329 patients who had undergone orchiopexy at this hospital when aged between 7 and 13.5 years were now over 18 years old. They were contacted by questionnaire. A total of 234 men (71%) returned the questionnaire and 142 of them agreed to provide a specimen of semen. Of the 142 patients, 48 had been operated on for clinically impalpable testes.

The sample of semen was collected after a 3-day period of abstinence. The entire sample was obtained by masturbation directly into a sterile container which had been pre-warmed to room temperature before use. The sample was delivered to the laboratory within 1 h of the ejaculation. Measurement of semen volume, density, motility and morphology was carried out according to the recommendations of Belsey *et al.* (1980). The mixed agglutination reaction (MAR) test was used for screening spermatozoa in fresh semen for antisperm antibodies (Stedronska and Hendry, 1983).

## Results

Of the 48 patients, 40 had unilateral and 8 had bilateral impalpable testes. Their mean age at orchiopexy was 9.9 years (range 7–13.6) and their mean age at follow-up was 25.8 years (range 18–41). The anatomical position of the testis in 40 men with unilateral impalpable testes on surgical exploration was as follows: abdominal (13), canalicular (21), absent or vanishing (6). The original position of 16 testes in 8 men with bilateral impalpable testes was abdominal (4), canalicular (9) and absent or vanishing (3).

Table 1 shows the results of semen analysis in 40 men with unilateral impalpable testes. This was normal in 27 men (67%); 4 had low sperm density but normal semen volume, motility and percentage of abnormal forms; 7 men had subnormal semen analysis and 2 were azoospermic.

The group of 40 patients with unilateral impalpable testes was further broken down. The results of semen analysis in the 6 men with unilateral absent or vanishing testes revealed that 3 had normal

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**Table 1** Results of Semen Analysis of 40 Men With Unilateral Impalpable Testes

| | | *Normal* | | *Subnormal* | |
|---|---|---|---|---|---|
| | *WHO Standards* | *Mean value* | *No.* | *Mean value* | *No.* |
| Volume (ml) | >1.5 | 2.7 | 34 | 0.6 | 6 |
| Density (×10$^6$/ml) | >20 | 62.8 | 27 | 8.3 | 11 |
| Morphologically abnormal forms (%) | <50 | 33 | 31 | 64 | 7 |
| Motility | >50 | 61 | 31 | 26 | 7 |

Two men had azoospermia.

seminal analysis, 1 had a low sperm count with normal volume and motility, 1 had a seriously abnormal analysis and 1 was azoospermic.

The Semen analysis in 13 men with unilateral abdominal testes is shown in Table 2. The semen analysis in 21 men with unilateral canalicular testes is shown in Table 3; in 18 cases (86%) this was normal. The semen analysis in 8 patients with bilateral impalpable testes revealed azoospermia in all.

The mixed agglutination reaction test showed evidence of antisperm antibodies in 1 patient with a unilateral impalpable testis; at operation he was found to have a vanishing testis.

**Table 2** Results of Semen Analysis of 13 Men With Unilateral Abdominal Testes

| | | *Normal* | | *Subnormal* | |
|---|---|---|---|---|---|
| | *WHO Standards* | *Mean value* | *No.* | *Mean value* | *No.* |
| Volume (ml) | >1.5 | 2.3 | 10 | 0.5 | 3 |
| Density (×10$^6$/ml) | >20 | 52.8 | 6 | 7.5 | 6* |
| Morphologically abnormal forms (%) | <50 | 38 | 9 | 67 | 3 |
| Motility | >50 | 58 | 8 | 23 | 4 |

*One man had azoospermia.

**Table 3** Results of Semen Analysis of 21 Men With Unilateral Canalicular Testes

| | | *Normal* | | *Subnormal* | |
|---|---|---|---|---|---|
| | *WHO Standards* | *Mean value* | *No.* | *Mean value* | *No.* |
| Volume (ml) | >1.5 | 3.1 | 19 | 0.8 | 2 |
| Density (×10$^6$/ml) | >20 | 68.5 | 18 | 11.2 | 3 |
| Morphologically abnormal forms (%) | <50 | 29 | 18 | 57 | 3 |
| Motility | >50 | 63 | 19 | 36 | 2 |

## Discussion

The outcome of treatment policies for orchiopexy has not been widely assessed and there are few follow-up studies to show that early orchiopexy is beneficial. Chilvers *et al.* (1986) reviewed 27 reports on adult fertility in terms of sperm density following diagnosis and/or treatment for undescended testes and concluded that there was little evidence that operation early rather than late (within the age range 4–14 years) had any effect on subsequent fertility. The outcome (in terms of fertility) of orchiopexy before the age of 2 years has not been evaluated adequately by follow-up. This is a relatively new policy and "carefully designed long-term follow-up studies" of early orchiopexy will not be available for at least 10 years. We have recently reported that the important factors for eventual fertility in cryptorchidism are not the timing of the operation but whether the condition is unilateral or bilateral (Puri and O'Donnell, 1988).

This study has shown that the subsequent quality of the semen in cryptorchid patients with impalpable testes depends on whether the condition is unilateral or bilateral. The semen quality of patients operated on for unilateral impalpable testes is good; 18/23 patients (86%) with unilateral impalpable canalicular testes had normal semen analysis. The semen of cryptorchid patients with bilateral impalpable testes is of poor quality; all such patients in our study were found to be azoospermic. Our data demonstrate a strong association between the original anatomical position of undescended testes and the subsequent quality of the semen.

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# Epidermoid Cyst (Monodermal Teratoma) of the Testis

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Summary—We report 14 patients with epidermoid cyst of the testis (monodermal teratoma). In 7 patients (5 treated within the last 5 years) the mass was excised and adjacent testicular tissue was biopsied. Seven patients underwent radical inguinal orchiectomy. Carcinoma *in situ* was not detected in any testicular tissue examined. There was no evidence of tumour recurrence in any patient after a mean follow-up of 10 years. Ultrasonographic appearance was not specific for a diagnosis of epidermoid cyst and exploratory surgery was required in all cases. Excision of the tumour and biopsy of adjacent testicular tissue to determine the presence or absence of carcinoma *in situ* is adequate treatment for this rare testicular neoplasm.

Epidermoid cyst of the testis is a rare, benign testicular tumour. It is generally regarded as a monodermal or monophasic teratoma. Fewer than 200 cases have been described in the literature and most of these have been case reports (Shah *et al.*, 1981; Murphy and Gaeta, 1986). Furthermore, the majority of these cases have been reported since 1980. It is estimated that epidermoid cyst of the testis represents less than 1% of all testicular tumours.

Opinion is divided as to the best treatment for this condition. The majority opinion favours excision of the tumour and preservation of the testis, although some recommend radical inguinal orchiectomy (Price, 1969; Berger *et al.*, 1985; Buckspan *et al.*, 1985; Schlecker *et al.*, 1985).

We reviewed the clinicopathological features of 14 patients with epidermoid cyst of the testis in order to assess local recurrence or metastasis during long-term follow-up, the presence of carcinoma *in situ* in testicular tissue adjacent to the tumour, and the accuracy of testicular ultrasonography in pre-operative diagnosis. We outline our recommendations for treatment.

## Patients and Methods

We reviewed the medical records of 15 patients with epidermoid cyst of the testis treated at the University of Minnesota Hospital and Clinic and the Department of Veterans Affairs Medical Center in Minneapolis. One patient was excluded from the study because there was insufficient preserved tissue for immunohistochemical analysis and so we could not determine whether he had carcinoma *in situ*.

Follow-up was calculated as the time from testicular biopsy or orchiectomy to the last urological examination. As part of the study, each patient was re-evaluated by a pathologist. Haematoxylin and eosin-stained slides were evaluated for tissue type, and the presence or absence of carcinoma *in situ* in adjacent seminiferous tubules was determined in all cases. Immunohistochemical studies for placental alkaline phosphatase were performed as described previously (Manivel *et al.*, 1989). Testicular ultrasonograms were available for 5 patients and were reviewed with a radiologist.

## Results

The mean age of the patients was 24 years (range 19–45). The ultrasonographic appearance of the tumour was hypoechoic in the 5 patients for whom

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ultrasonograms were available. The tumour wall was smooth in 3 cases and irregular in 2; the size of the tumours ranged from 5 mm to 3 cm (Fig. 1).

The mean length of follow-up was 10.6 years (range 2 months–22 years). No patient had a recurrence during follow-up. One died of causes not related to his treatment for an epidermoid cyst and autopsy revealed no evidence of testicular tumour. The type of surgery performed—radical inguinal orchiectomy on 7 patients, inguinal excisional biopsy on 4 and trans-scrotal excisional biopsy on 3—did not influence the outcome.

The histological appearance of the tumours was characteristic of epidermoid cysts; they contained keratinous material and were lined by mature stratified squamous epithelium. No other teratomatous or germ cell elements were identified. Carcinoma *in situ* was not detected in testicular tissue from any of the 14 patients.

## Discussion

The histogenesis and nosological position of epidermoid cysts of the testis are not finally established. Although they are not included in the histological classification of the World Health Organization on testicular tumours, the current prevailing hypothesis is that they are of germ cell origin and represent monodermal teratomas (Mostofi and Sobin, 1977). Although the distinction between epidermoid cysts and cystic teratomas may be artificial, we recommend the use of the former designation only for those tumours in which thorough sampling has failed to reveal elements other than mature squamous epithelium and keratin. Epidermoid cyst of the testis is also characterised by the absence of carcinoma *in situ* in seminiferous tubules adjacent to the cyst (Manivel *et al.*, 1989). If, in addition to a squamous lining, cutaneous adnexa, other types of epithelium or mesenchymal elements are also recognised, the tumour should be classified as a teratoma and thus potentially malignant. In almost all instances, patients with mature teratoma will also have carcinoma *in situ* in the ipsilateral testis.

If the epidermoid cyst (monodermal teratoma) is a benign lesion, it should be possible to preserve the testis if the nature of the entity is recognised at surgery. These lesions do not involve the tunica, they look exactly like epidermoid cysts found elsewhere in the body and they can be easily enucleated from the surrounding testicular tissue. The transected cyst has a smooth wall and is packed with keratinous debris. In the 5 years since we recognised this lesion as being more common than previously thought, we have treated 5 patients with cyst enucleation, testicular biopsy and testicular preservation. There have been no instances in which a malignant tumour was mistaken for an epidermoid cyst. It should be emphasised, however,

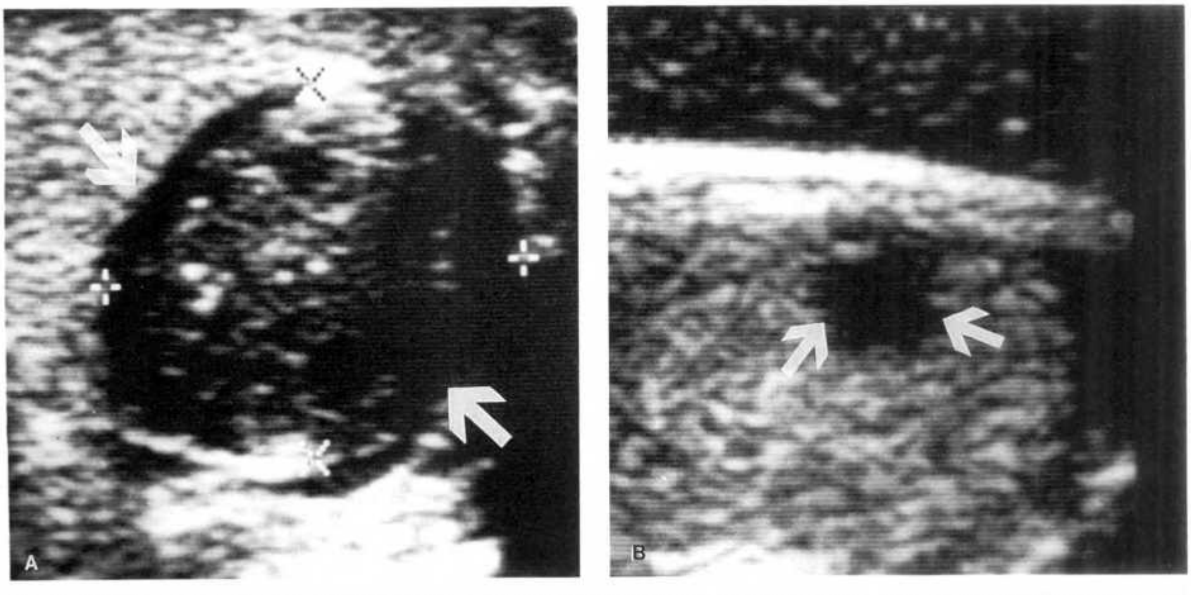

**Fig. 1** (A) Ultrasonogram of an epidermoid cyst. Large mass is hypoechoic with a distinct capsule (arrows). (B) Ultrasonogram of an epidermoid cyst. Small mass is hypoechoic with an irregular capsule (arrows).

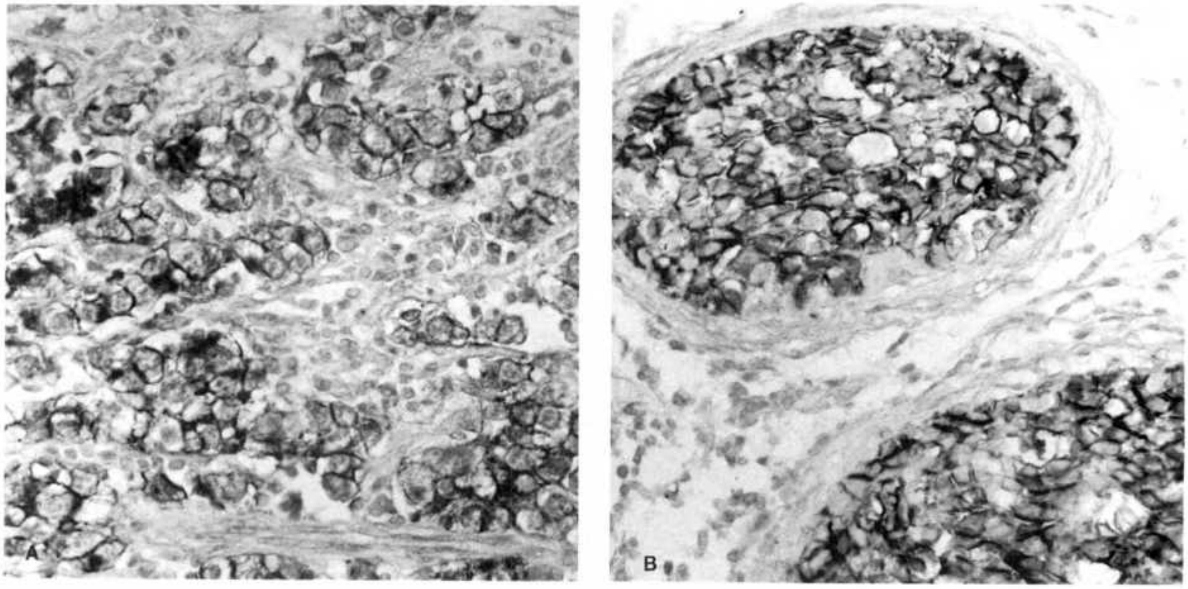

**Fig. 2** Intense cytoplasmic membrane immunoreactivity for placental alkaline phosphatase (A) in seminoma cells and (B) in intratubular germ cell neoplasia.

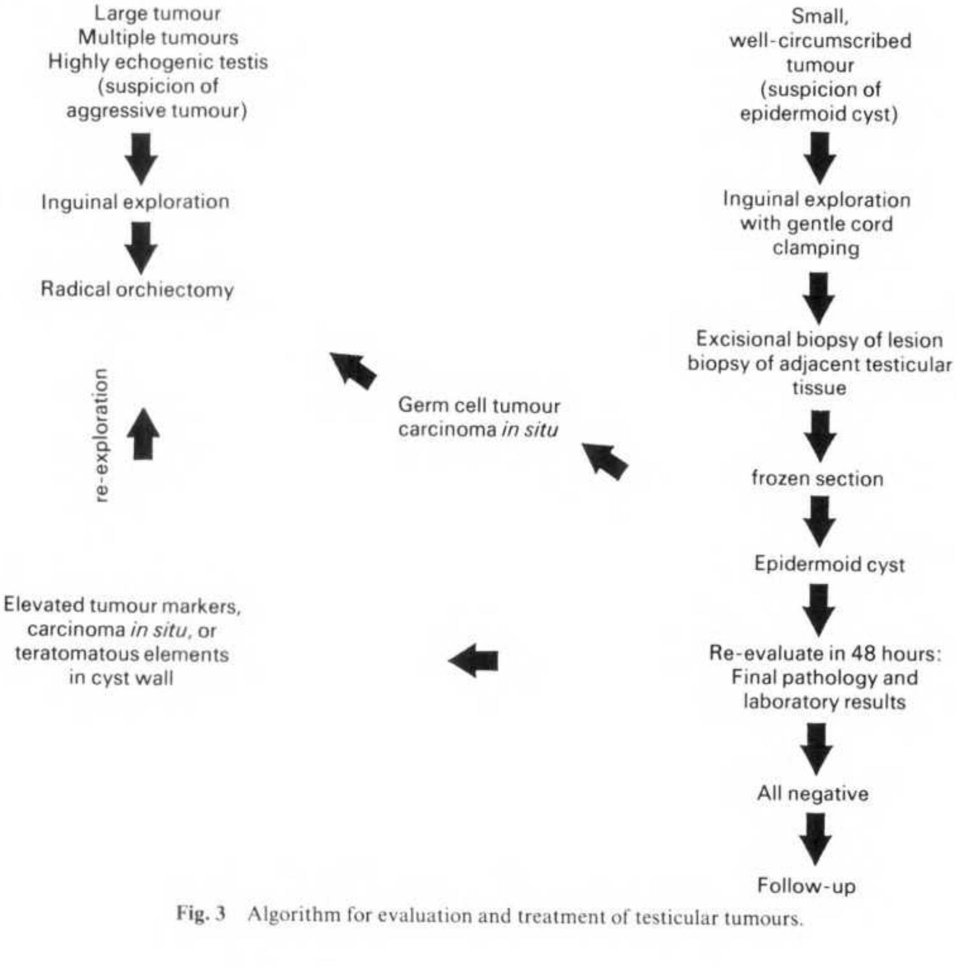

**Fig. 3** Algorithm for evaluation and treatment of testicular tumours.

that all solid lesions within the testis should be presumed to be malignant and evaluation should always be made with the testis isolated and the wound protected from potential tumour spillage.

The ultrasonographic appearance of an epidermoid cyst may support the diagnosis, but it is not specific and may be misleading, as illustrated by the following case.

A 22-year-old man with a testicular mass underwent testicular ultrasonography which revealed a small, sharply demarcated mass on the testicular surface suggestive of an epidermoid cyst. During inguinal exploration a small, easily enucleated mass was detected on the testicular surface. Analysis of a frozen tissue section revealed seminoma. Radical orchiectomy was performed and subsequent pathological examination of the resected testis revealed scattered carcinoma *in situ* (Fig. 2).

Nevertheless, for the following reasons we continue to recommend ultrasonography as the initial diagnostic test after physical examination has indicated a testicular abnormality. If the ultrasonographic appearance is consistent with an epidermoid cyst of the testis (hypoechoic, well demarcated intratesticular lesion), inguinal exploration and an excisional biopsy are performed. If frozen section analysis of the cyst reveals characteristics of an epidermoid cyst, 2 biopsies of adjacent testicular tissue are obtained; one is fixed in formalin and the other in Bouin's or Cleland's solution (Reinberg *et al.*, 1989). If pathological examination of the remainder of the specimen reveals teratomatous elements within the cyst wall or carcinoma *in situ* in adjacent testicular tissue, re-exploration and radical orchiectomy are performed.

The presence of carcinoma *in situ* correlates strongly with the potential for aggressive behaviour of a testicular germ cell tumour; however, carcinoma *in situ* can be missed in frozen sections and immunohistochemical staining of permanent sections may be required to confirm the diagnosis (Manivel *et al.*, 1989; Reinberg *et al.*, 1989).

Our treatment programme for patients with a suspected epidermoid cyst of the testis is outlined in Figure 3. In our experience, transinguinal partial orchiectomy is adequate treatment. A small percentage of these patients will require re-exploration and radical orchiectomy if other teratomatous or germ cell elements or carcinoma *in situ* are identified after thorough sampling of the specimen. The possible need for additional surgery is explained to all patients before the initial surgical exploration. Adjuvant hemi-scrotectomy may be necessary if there is subsequent evidence of scrotal contamination from the testicular biopsy.

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# Comparison of Urethral Reaction to Full Silicone, Hydrogen-coated and Siliconised Latex Catheters

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Summary—Indwelling urinary catheter may induce an inflammatory reaction or even stricture of the urethra. Catheter encrustation and urinary infection are other disadvantages associated with long-term catheterisation.

In the present study, 77 male patients were catheterised randomly as part of their normal treatment with 1 of 3 different types of catheter: 22 siliconised latex, 28 hydrogel-coated latex and 27 full silicone catheters. The mean duration of catheterisation was 2.2 days. The urethral inflammatory reaction was assessed from cytological urethral swab specimens. Catheter encrustation was studied using scanning electron microscopic (SEM) analysis.

The full silicone catheters induced the mildest degree of inflammation in the urethra, the percentage mean of inflammatory cells in smears being 20%. In both latex catheter groups the value was 36%. Neither the age of the patients nor the duration of catheterisation had any effect on the inflammatory reaction, which was more marked in patients with haemodynamic abnormalities. The hydrogel coating effectively prevented encrustation, while siliconised latex catheters were the least resistant to encrustation.

The inflammatory reaction was variable in all patients. The use of urethral catheters should be restricted and suprapubic tubes should be used instead, particularly in patients with shock-like circulatory changes. By developing the biocompatibility and physical properties of urinary catheters, more compatible devices may be manufactured.

It is well known that urinary catheters may cause urethritis and urethral strictures. The reaction varies according to the type of the catheter used. Uncoated rubber catheters are the most irritative and full silicone and PVC catheters the best tolerated (Binder and Conick, 1969; Painter *et al.*, 1971; Edwards and Trott, 1973; Bruce *et al.*, 1976). Talja *et al.* (1986) and Nacey *et al.* (1986) have described a correlation between the *in vitro* cell culture toxicity of urinary catheters and the *in vivo* urethral epithelial destruction and inflammatory reaction.

Catheter encrustation is another common problem associated with the long-term use of indwelling catheters. Encrustation begins with the adherence of inflammatory products and leads to mineralisation. In addition to the infective status (Lome and Navani, 1970) and implantation period, encrustation is also influenced by the catheter material. Full silicone, silicone elastomer-coated and PVC catheters are the most resistant to encrustation (Binder and Conick, 1969; Srinivasan and Clark, 1972; Bruce *et al.*, 1974).

Latex catheters coated with hydrogel have recently been introduced (Biocath, Bard Ltd). This coating absorbs water to make the surface soft and slippery. It is therefore less damaging to the urethra and may resist encrustation.

The aims of the present study were to resolve the effect of indwelling catheter material on the urethral inflammatory reaction and on the adherence of inflammatory products to catheters. Other possible causes were also investigated.

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## Patients and Methods

The study group comprised 77 consecutive male patients aged between 17 and 84 years (mean 58.7). They were catheterised as part of their routine treatment and 3 different types of catheter (size 14F) were used (Table 1).

To evaluate the urethral inflammatory reaction induced by the indwelling catheters a modification of the method described by Edwards and Trott (1973) was used. Cotton wool swab specimens were taken from the penile urethra before catheterisation, after removal of the catheter and on the second or third day after removal. The specimens were taken by rubbing the swab against the anterior wall of the urethra 5 cm proximal to the external orifice. Smears were made and attained according to the Papanicolaou method, covered with a glass slide and analysed. The ratio between inflammatory cells and epithelial cells was determined and the result recorded as a percentage of the inflammatory cells from the total cell count.

To assess the adherence of inflammatory products on the surface of the catheters, 1-cm lengths were taken from 41 catheters and viewed with a scanning electron microscope (Jeol JSM-35C). The results were categorised as (1) epithelial cells, (2) inflammatory cells and (3) mucus/fibrin deposits. Control specimens were taken from catheters that had not been used in patients.

For SEM analysis, 1-cm lengths of catheter were divided longitudinally, air dried and fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer for 12 h. The specimens were dehydrated in ethanol and critical point dried in a Balzer Union CPD 020 Critical Point Dryer according to the recommendations of Andersson (1951). The unimplanted control specimens were vacuum dried and coated with 200 Å thick gold in a Jeol Fine Coat Ion Sputter JFC-1100 (1.2 kV, 5–10 mA, 6 min) for viewing (acceleration 4–6 kV). Photographs with different magnifications were taken and analysed.

One-tailed analysis of variance (Fisher's F-distribution) and Spearman's rank correlation coefficient tests were used.

**Table 1** Patients and Categories

| *Catheter* | *No. of patients* | *Mean age (years)* |
|---|---|---|
| Siliconised latex | 22 | 60.5 |
| Hydrogel-coated latex | 28 | 57.8 |
| Full silicone | 27 | 58.9 |

## Results

No inflammatory reaction was seen in the specimens taken before catheterisation (Fig. 1). In the specimens taken immediately after catheter removal an inflammatory cell reaction was seen in nearly all cases (Fig. 2). It was most abundant in

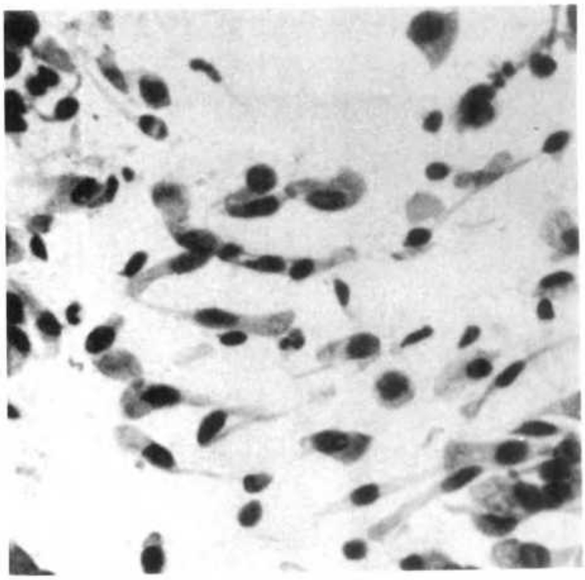

**Fig. 1** Specimen from normal urethra with no contact with indwelling catheter. Detached epithelial cells with homogenic nuclei. (Light microscopic view × 400).

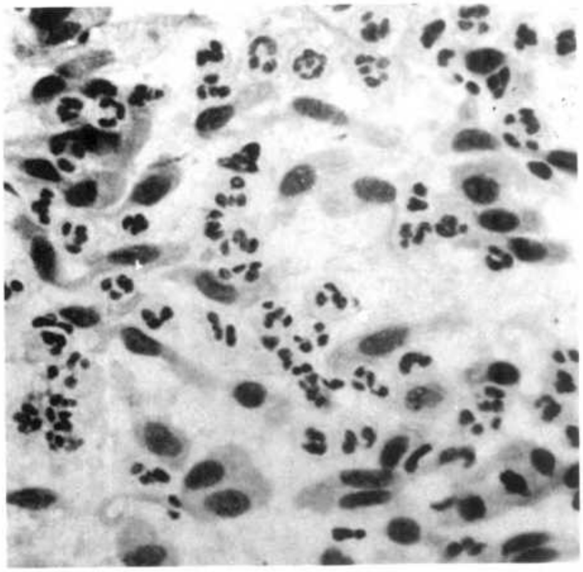

**Fig. 2** Specimen from urethra after catheter removal. Most of the cells are composed of polymorphonuclear leucocytes. Some epithelial cells are multinucleated. (Light microscopic view × 400).

both of the latex catheter groups (36%) and less prominent in the full silicone group (20%) (Table 2). The difference was statistically significant ($P$ $<0.05$). Fisher's F-distribution). In the acute phase, 80 to 90% of the inflammatory cells were neutrophilic granulocytes and mononuclear cells were in the minority (Fig. 2). The inflammatory reaction had subsided almost completely by the second or third day.

In SEM analysis, detached epithelial cells were seen on the outer surface of all catheters (Figs. 3A and 4A). The accumulation of inflammatory cells

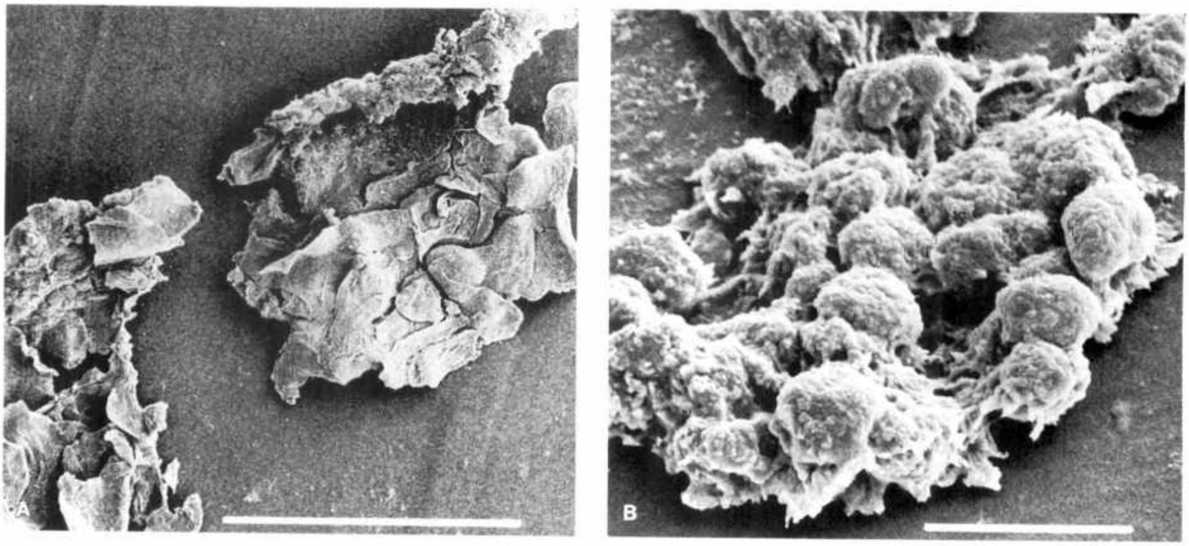

**Fig. 3** (A). Detached epithelial cells on full silicone catheter. The surface of the catheter is very smooth and some longitudinal glow ridges induced by folding are seen. Bar = 100 μm. (SEM × 350). (B). Clumps of inflammatory cells and mucus together with fibrin deposits on the surface of full silicone catheter. Bar = 10 μm. (SEM × 2500).

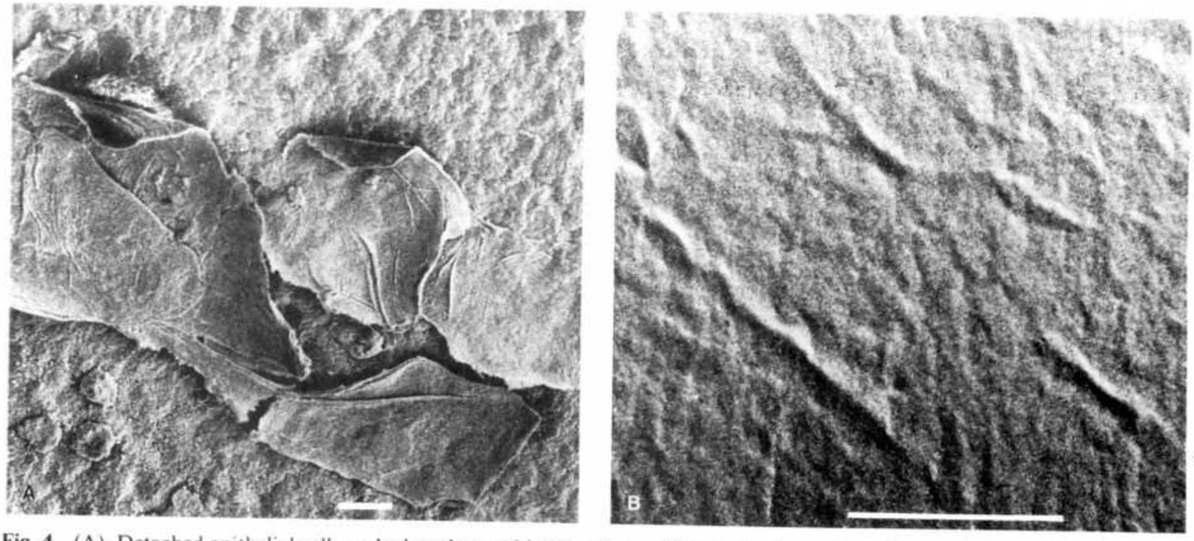

**Fig. 4** (A). Detached epithelial cells on hydrogel-coated latex catheter. The coating is rough and in some places partly loosened because of fixation for SEM. Bar = 10 μm. (SEM × 700). (B). Hydrogel-coated latex catheter without fixation artefacts. The contour is smooth and gently folded. Bar = 100 μm. (SEM × 300).

**Table 2** Effect of Catheter Material on Urethral Inflammatory Cell Reaction ($P < 0.05$, Fisher's F-distribution)

| *Catheter* | *No. of patients* | *Mean ± SEM* |
|---|---|---|
| Siliconised latex | 22 | 36 ± 6.1 |
| Hydrogel-coated latex | 28 | 36 ± 6.5 |
| Full silicone | 27 | 20 ± 4.0 |

**Table 3** Effect of Indications for Catheterisation on Inflammatory Reaction ($P < 0.05$, Fisher's F-distribution)

| *Indications* | *No. of patients* | *Mean ± SEM* |
|---|---|---|
| Myocardial infarct | 9 | 44 ± 14 |
| Intensive care unit patient with other indications | 24 | 39 ± 4.9 |
| Lower extremity vascular surgery | 16 | 27 ± 6.8 |
| Other major surgery | 22 | 17 ± 4.2 |

and mucous deposits was least in the hydrogel-coated latex group (Fig. 4A). Both deposits were seen to cover the siliconised latex catheters in particular, occasionally in large conglomerates (Figs. 5A and 5B). The inflammatory deposits on the outer surface of the full silicone catheters were closer to those of the hydrogel-coated latex than the siliconised latex catheters (Fig. 3B).

The preparation of the latex catheter samples indicated that despite careful ethanol cascade dehydration, water remained and gas bubbles were formed in the catheters during critical point drying. This led to the destruction of the outer contour of the catheters in some places but did not affect assessment of the changes. Thus we correlated the vacuum dried, control specimens with the critical point dried, indwelling specimens. It was also seen that the outer contour of the hydrogel coated catheters was rough after critical point drying (Fig. 4A). In the vacuum dried control specimens the outer surface was quite smooth (Fig. 4B). The silicone oil covering was seen to melt from the siliconised catheters in a few days (Fig. 5C).

Neither the patients' age nor the duration of catheterisation (1–4 days, mean 2.2) had any effect on the inflammatory reaction seen in the specimens. On the other hand, the indications for catheterisation did have an effect ($P < 0.05$ Fisher's F-distribution) (Table 3). The reaction was most significant in patients whose systemic circulation was deficient due to myocardial infarction, severe septic shock, severe intoxication, etc.

## Discussion

The results show that the physical properties of urinary catheters can be developed to make the

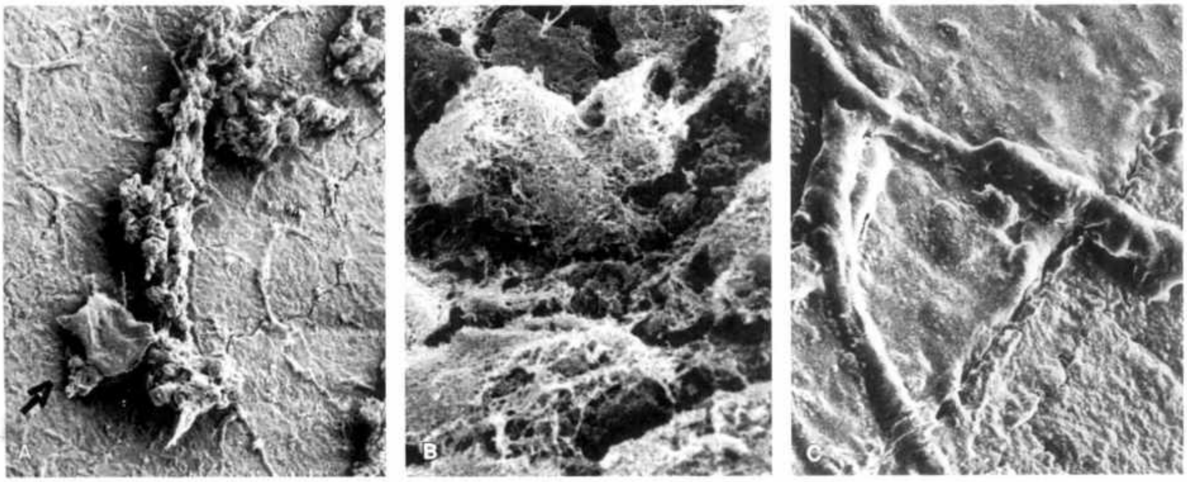

**Fig. 5** (A). Clumps of leucocytes and mucus on siliconised latex catheter. One detached epithelial cell can be seen (arrow). The silicone oil coating is melting after a few days' implantation. Bar = 10 µm. (SEM × 400). (B). Leucocyte and fibrin deposits on rough surface of siliconised latex catheter. Bar = 10 µm. (SEM × 1300). (C). Melting silicon oil on siliconised latex catheter. Bare latex in contact with tissue. Some grooves on catheter surface caused by manufacturing process are also seen. Bar = 10 µm. (SEM × 1000).

devices more resistant to the accumulation of inflammatory products on the surface. The hydrogel coating decreases friction between the catheter and the urethral epithelium and prevents inflammatory products from adhering to the outer surface of the catheters; this may be the first step in preventing encrustation. Hydrogel coating has been shown to be as resistant as full silicone to struvite and calcium phosphate encrustation, with exposure times of 18 weeks having been used (Cox *et al.*, 1988). Hedelin *et al.* (1987) found that hydrogel coating of latex catheters was more effective against encrustation than full silicone.

The proper fixation of specimens for SEM analysis was a problem. Preliminary investigations showed that latex and hydrogel coatings absorb water. During ethanol dehydration different methods were used, *e.g.* varying the incubation times and concentrations to remove the water. This is difficult even in a vacuum desiccator (Cox *et al.*, 1988). For indwelling catheters, vacuum drying was not used owing to a shortage of suitable instruments. The only fixation artefacts were roughness of the hydrogel coating (Fig. 4A) and transient distortion of the specimens caused by retained water in latex during critical point drying. It is obvious that the artefacts did not influence the inflammatory accumulations on the surface of the catheters. The vacuum dried, non-indwelling hydrogel-coated latex catheters were smooth when viewed by SEM (Fig. 4B). We would, however, prefer vacuum or freezing methods (Cox, 1990) for the dehydration of moisturised latex products.

A similar inflammatory cell reaction was induced in the urethra by both types of latex catheter (Fig. 2) and was more pronounced than that induced by the full silicone catheters. The difference was significant ($P<0.05$). It is known that several chemicals are used during the manufacture of latex catheters. Could they be responsible for this inflammation? Zinc-containing degradation products of latex accelerators and volatile N-nitrosamines have come under suspicion (Heenan *et al.*, 1989). A correlation has been shown between *in vitro* cell culture toxicity of catheter eluates and *in vivo* urethral inflammatory reaction induced by catheters (Nacey *et al.*, 1986; Talja *et al.*, 1986).

The catheters used in the present work were suitable for clinical use (*i.e.* non-toxic) according to a cell culture tissue toxicity test based on DNA synthesis inhibition (Ruutu *et al.*, 1985). It has been shown that latex causes an inflammatory reaction in the urethra although, according to the toxicity testing methods, it should be non-toxic (Nacey *et al.*, 1986; Talja *et al.*, 1986). In earlier studies the inflammation consisted mainly of eosinophilic granulocytes in the histological sections (Talja *et al.*, 1986; Goble *et al.*, 1989), but in the present study only a few eosinophils were seen and 80 to 90% of the cells were neutrophilic granulocytes. The rapid subsidence of the inflammatory reaction a few days after catheter removal is in accordance with the findings of Andersson (1979).

The duration of catheterisation had no effect on the grade of inflammatory cell reaction, which began soon after implantation. The findings by Talja *et al.* (1986) concerning catheter-induced changes in the urethra were seen after an implantation time of 6 h. Nacey *et al.* (1986) found no increase in the reaction after an implantation time of 24 h. Edwards and Trott (1973) found that this reaction subsided after a week if implantation continued. Similarly, the age of the patients had no effect on the inflammatory reaction. In the epidemics of the urethral strictures reported by Ruutu *et al.* (1984), the youngest patients were 30-year-old men. In the present study the youngest patient was a 17-year-old boy.

The similarity between the results of the stricture epidemics after open heart surgery and those of the present work lay in the increase of inflammation in the urethra under circumstances where the blood circulation in the urethra was decreased. Patients with myocardial infarcts and other life-threatening problems have shock-like circulatory changes with peripheral vasoconstriction. This exacerbates the inflammation induced by the chemicals dissolved from latex because the chemicals accumulate in the urethral epithelium and may lead to stricture formation (Talja *et al.*, 1986). The inflammation is mediated by complement activation (Talja *et al.*, 1986; Garred *et al.*, 1989).

The hydrogel-coated latex catheter is an interesting new product and is recommended for long-term use because of its ability to prevent encrustation. The hydrogel-coated catheter is most suitable in suprapubic cystostomies and in female patients because of its inflammation-inducing properties. In the male urethra this inflammation may be harmful. The hydrogel coating has bad insulating properties for water soluble chemicals dissolving from the latex core. Further studies are needed to estimate the induction of inflammation in the urethra *in situ*, since full silicone may also induce moderate inflammation. Thus suprapubic catheters are best for long-term catheterisation.

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# Case Reports

## Haemospermia as a Presenting Symptom of Lymphoma

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Haemospermia is usually not associated with serious disease and is, therefore, frequently considered to be a symptom of limited significance. We present a case of Hodgkin's lymphoma in which haemospermia was one of the dominant presenting symptoms.

### Case Report

S.A., a 29-year-old male, presented with a 4-month history of haemospermia which was recently associated with a vague lower abdominal ache and erectile failure. He also reported an 18-month history of night sweats and gradual weight loss. Physical examination was normal. Routine haematological assessment revealed an elevated ESR of 107 mm/s and a low haemoglobin of 10.3 g%. Coagulation studies were normal. Intravenous urography showed medial displacement of the left ureter and left wall of the bladder (Fig.). Ultrasonography and CT scan demonstrated that this was due to left iliac lymphadenopathy and that the para-aortic and peri-pancreatic nodes were similarly enlarged. There was no evidence of supradiaphragmatic involvement. Biopsy of a left iliac lymph node showed Hodgkin's lymphoma of mixed cellularity; chemotherapy was commenced, with an early favourable response that included complete resolution of the haemospermia.

### Comment

Haemospermia has been associated with a variety of inflammatory, traumatic and neoplastic disorders of the genitourinary tract (Parker, 1942). Investigation should reveal a cause in 30% of cases (Fletcher *et al.*, 1981). It has been reported in association with non-urinary tract disease on a number of occasions, but never before with lymphoma. Presumably in this case the haemospermia was due to direct invasion of the seminal vesicles by the malignant lymphadenopathy; the disappearance of the haemospermia following chemotherapy tends to support this view.

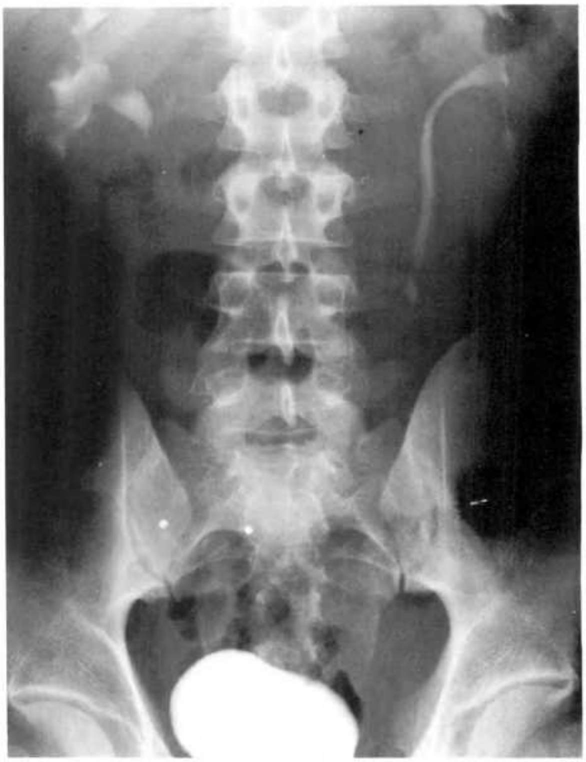

Fig.

In younger men in particular, haemospermia is often regarded as being of little significance, especially if there are no associated symptoms. This case illustrates that it may be associated with serious or life-threatening disease and should therefore be subjected to full evaluation (Marshall and Fuller, 1983).

### Acknowledgements

We thank Dr Carr, Dr Finney and Mr Thomson for their kind permission to prepare this report.

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# Carcinoma of the Bronchus and Metastases from an Occult Testicular Tumour

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## Case Report

A 58-year-old patient had a right upper lobe lung resection in September 1987 for poorly differentiated mixed adenosquamous carcinoma T1NO which was originally found on routine chest X-ray. In October 1988 an excisional biopsy was done on an enlarged right supraclavicular node which showed poorly differentiated carcinoma with clear cell change and some squamous differentiation compatible with the original lung tumour.

Chest X-ray (Fig. 1) at this time showed recurrence of the tumour in the right lung with prominent right hilar, right lung and mediastinal masses. The patient was referred for radiotherapy for early superior vena cava obstruction for which he received 3250 cGy in 10 fractions by an AP parallel opposed pair to mediastinum, using a 4 MV linear accelerator. The patient was well until December 1988, when he was admitted as an emergency with symptoms of cerebral metastases. These were confirmed by CT scan. A routine chest X-ray at this time had shown a marked change, with the appearance of metastases in both lungs (Fig. 2). This patient was known to have had an undescended right testis since birth and he underwent an exploratory operation at the age of 2 weeks, although orchiopexy was not performed. He lost his left testis in 1985 with a left-sided hernia repair and had remained on testosterone replacement since that time. A $\beta$HCG was checked and this showed a level of 5640 iu/l, suggestive of germ cell tumour. The patient died 1 day before receiving the laboratory report. No post mortem was allowed.

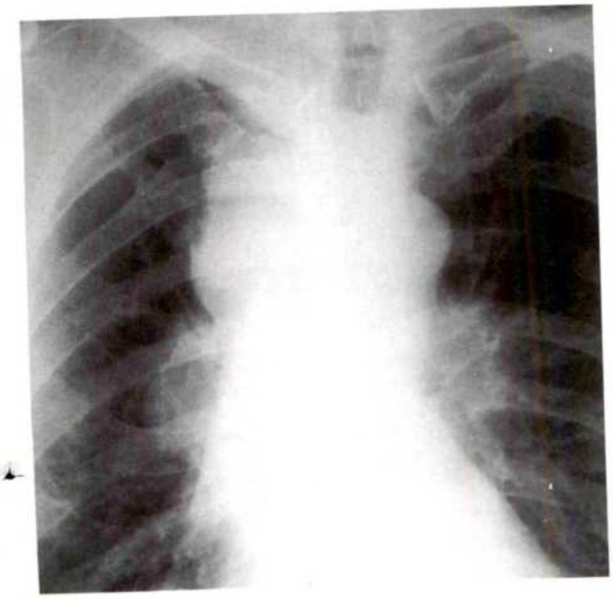

Fig. 1

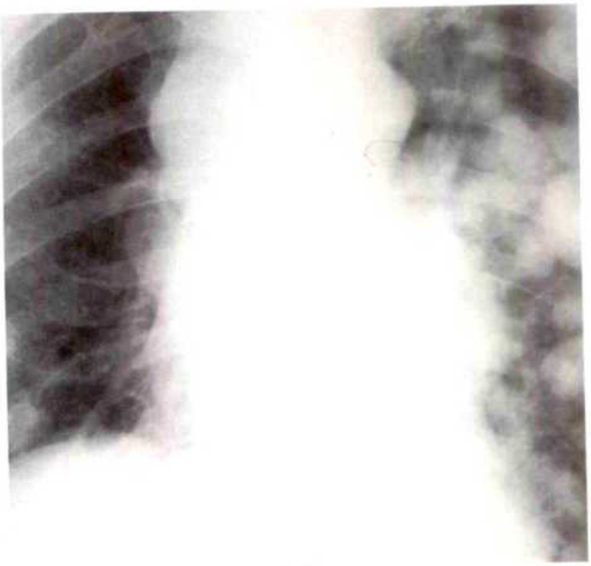

Fig. 2

## Comment

This patient's routine chest X-ray showed a cavitated rounded shadow at the periphery of his right lung mid-zone, 2 cm in diameter. The probability of his 5-year survival after lobectomy would have been 72 to 77% of patients with similar tumours (Hashimoto *et al.*, 1986; Little *et al.*, 1986). His prognosis when he developed lymph node metastasis became poor and he would probably have died within 1 year if he had developed no other primary tumour. When he presented with symptoms suggesting metastases in the brain and the liver, he was expected to die within 3 or 4 weeks. Further investigations would have been futile, knowing that his bronchogenic carcinoma was of adenosquamous type. Only the shape, size and multiplicity of the metastases in both lungs suggested that they came from a testicular tumour. No chemotherapy was given; the $\beta$HCG report was received 1 day after the patient's death.

Within the limitations of the database, we could find no reference to a case of primary bronchogenic carcinoma, primary testicular tumour and metastases of testicular tumour in the lung.

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# Necrotising Testicular Vasculitis Associated with Dermatomyositis

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## Case Report

A 7-year-old boy with a 4-year history of dermatomyositis was admitted for investigation of microscopic haematuria. He was currently being treated with prednisolone, cyclosporin A and nifedipine. During admission he developed right-sided lower abdominal pain. Examination revealed a mild pyrexia of 37.2°C, lower abdominal tenderness and a swollen, tender, red scrotum on the right side. The clinical diagnosis of acute testicular torsion was made. At operation, the dartos was discoloured and the tunica vaginalis and testis were black. There was no apparent twist in the cord. A right orchiectomy and contralateral plication were performed. Post-operative recovery was satisfactory.

Histological sections showed massive haemorrhage into the tunica albuginea and testis, although the seminiferous tubules were well preserved (Fig.). Arteries and veins in the testis showed fibrinoid necrosis with leucocytoclasis and occasional fragmentation of the elastic lamina. A histological diagnosis of leucocytoclastic vasculitis was made; these were not the histological appearances of acute torsion.

At follow-up 3 months later all wounds had healed well and the left testis was normal.

## Comment

Necrotising vasculitis affecting the testis is a rare manifestation of systemic vascular disease, the commonest of which is polyarteritis nodosa (Shurbaj and Epstein, 1988). It is believed that this is the first reported case associated with dermatomyositis in which the arteritis primarily involves the skin and muscle. Other reported sites involved with dermatomyositis are the gastrointestinal tract, nervous system and adipose tissue (Shanks and Goll, 1984).

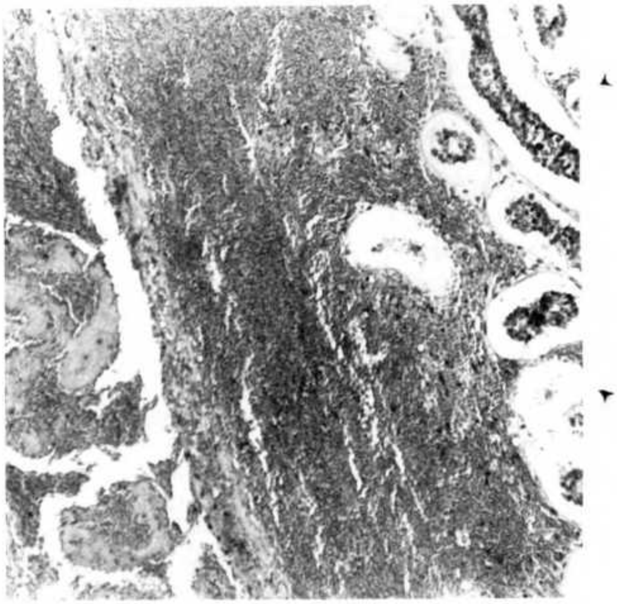

**Fig.** Fibrinoid necrosis of vessels at periphery of testis with well preserved seminiferous tubules. (H and E × 40).

The histological appearance of leucocytoclasis and fragmentation of the elastic lamina are not associated with any of the drugs used in this patient (Bergstrand and Bohman, 1985) and there had been no recent change in the therapeutic regime.

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## Beware of Antacids!

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An unusual and probably preventable cause of urinary tract calculus is described.

### Case Report

A 36-year-old female accounts clerk presented with her first episode of renal colic. An intravenous urogram demonstrated a calculus measuring approximately 3 mm at the left pelviureteric junction. After a period of 4 days' conservative management, a plain abdominal X-ray showed descent of the stone into the ureter.

After discharge the patient carefully sieved her urine. At a subsequent out-patient attendance, she presented a stone (4 × 2 × 2 mm) that she had passed. Plain abdominal X-ray revealed that she was stone-free. In the laboratory it was noted that the stone was particularly hard to grind with a mortar and pestle. Infra-red spectroscopic analysis of the stone suggested a composition of silicon dioxide. X-ray energy dispersive spectroscopy confirmed that the bulk of the stone was silicon.

At a later interview, the patient volunteered that she regularly purchased magnesium trisilicate oral compound BP and took this for "acidity", initially 1 teaspoon with every meal for at least 2 years and thereafter as required over a period of 15 years.

### Comment

Silicon stones in the urinary tract are rarely reported (Levison *et al.*, 1982). In this case it is likely that the stone was caused by the ingestion of magnesium trisilicate over a long period. When the association of a silicon stone and antacid excess is found, the indications for antacid therapy should be carefully assessed and discontinuation or conversion to a silicon-free antacid considered.

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## Inverted Papilloma of the Penile Urethra

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Inverted papillomas are rare, benign, polypoidal urothelial lesions originally described by Potts and Hirst in 1963. Over 90% occur within the urinary bladder and particularly in the bladder neck and trigone (Lazarevic and Garrett, 1978). Extravesical lesions are particularly unusual and no report has been found of an inverted papilloma occurring in the penile urethra.

### Case Report

A 58-year-old man presented with episodes of painless haematuria, a deterioration in urinary stream, hesitancy and terminal dribbling. There was no significant past medical history and physical examination was unremarkable. Full blood count, urea and electrolytes, mid-stream urine and intravenous urography were normal. At urethroscopy a 5-mm papillary lesion was found in the penile urethra, several centimetres distal to the penoscrotal junction. The lesion was removed with biopsy forceps and the base lightly fulgurised. The lateral lobes of the prostate were moderately occlusive and the bladder was normal. The urethra was normal at endoscopic follow-up 9 months later.

The specimen (Fig.) was a tumour with the characteristics of a transitional cell papilloma, but with an endophytic rather than exophytic growth pattern typical of an inverted papilloma.

### Comment

Inverted papillomas are rare benign lesions occurring in transitional epithelium. Over 50% occur within the trigone and bladder neck (Lazarevic and Garrett, 1978). They are found in or extending from the prostatic urethra (DeMeester *et al.*, 1975) but have not been described in the penile urethra. The majority of patients are male with a peak incidence in the sixth and seventh decades. The lesions are usually single, but may be multiple or occasionally coexist with transitional cell carcinoma. Haematuria is the most common presenting symptom, but patients may have a degree of bladder outflow obstruction if the papilloma is within the bladder

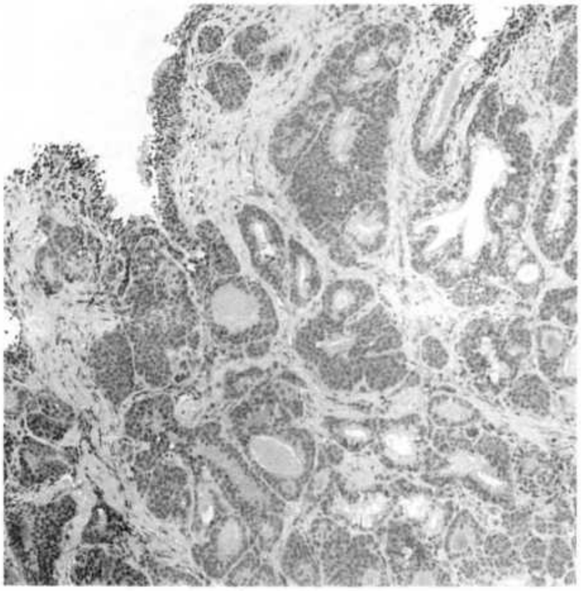

**Fig.** Section through the 5-mm inverted papilloma excised from the penile urethra. Magnification × 100. Haemotoxylin and eosin.

neck or prostatic urethra. Inverted papillomas seem to be benign, with few reported instances of recurrence following resection and fulguration of the base (DeMeester *et al.*, 1975). The aetiology is unknown but the tumour is considered to be neoplastic. The finding of an inverted papilloma in the penile urethra coupled with previous descriptions in the renal pelvis and ureter are at odds with the ideas of Potts and Hirst (1963) that they develop from subtrigonal glands.

## Acknowledgement

We thank Dr C. Tzannotos for the photograph.

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# Phimosis Associated with Mycosis Fungoides

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## Case Report

A 32-year-old man presented to the surgical unit from the dermatological out-patient clinic with a 2-week history of poor stream and severe urinary frequency. He had suffered from mycosis fungoides for 11 years. Treatment had included chemotherapy, radiotherapy, psoralen ultraviolet A (PUVA) and electron beam therapy for widespread lesions, including some on his scrotum.

On examination, he had a tight phimosis but the foreskin itself appeared healthy and his penis and scrotum appeared normal.

A circumcision was performed with considerable difficulty. There was a pinhole opening in the foreskin which was fused to the glans in several places. The foreskin was retracted with difficulty, resulting in avulsion of skin from the surface of the glans penis.

He made an uneventful recovery and was passing urine without difficulty when discharged.

Histology of the foreskin (Fig.) revealed an infiltrate of

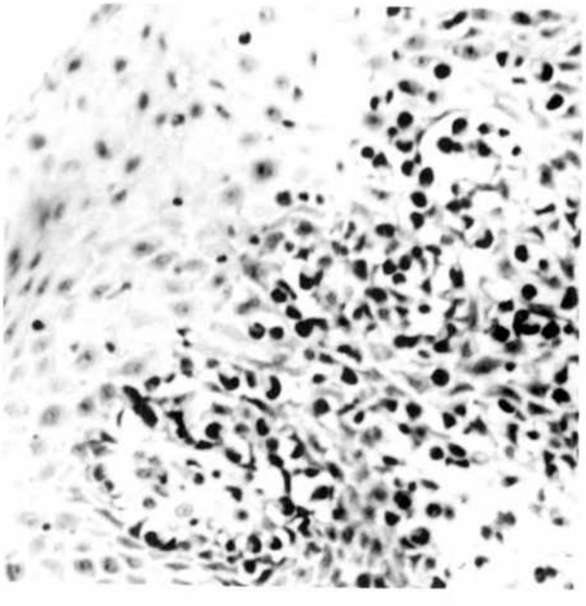

**Fig.** Epidermal lymphoid infiltrate including many mycosis cells with clear surrounding haloes and forming Pautrier's abscesses. (H and E × 100).

lymphoid cells in the epidermis and upper dermis with Pautrier's microabscesses. This was consistent with epidermotrophic mycosis fungoides at the plaque stage. This diagnosis was supported by immunohistochemical techniques. The appearance was similar to that of recent forehead skin biopsies. There was no evidence of other disease processes or post-radiotherapy changes.

## Comment

This is the first reported case of phimosis due to mycosis fungoides.

It is reported that lichen sclerosus et atrophicus (also known as balanitis xerotica obliterans) (Campus *et al.*, 1984) is the only common skin disease associated with phimosis (Chalmers *et al.*, 1984). In the presence of generalised skin disease the foreskin may be involved, even if the external appearance is normal, as in this case.

In these circumstances circumcision may be difficult and should be performed by an experienced surgeon.

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# Osteogenic Differentiation in a Sarcomatoid Renal Carcinoma

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A case of a sarcomatoid renal carcinoma which underwent osteogenic differentiation is presented. Only 5 previous similar cases have been reported.

## Case Report

A 47-year-old lady was admitted with a 3-month history of intermittent haematuria and left loin pain. Examination revealed a large ballotable mass in the left hypochondrium. A plain abdominal X-ray revealed a huge soft tissue mass with areas of dystrophic calcification. An IVU and DMSA scan showed the left kidney to be non-functioning and ultrasound confirmed the abnormal calcification.

Nephrectomy yielded a specimen weighing 2000 g and measuring 26 × 17 × 13 cm. Macroscopically, the kidney was largely replaced by lobulated grey tumour which contained areas of calcification and haemorrhagic necrosis. Histologically, the tumour consisted of spindle cell areas with pleomorphic giant cells surrounding malignant osteoid and immature bone (Fig.). Extensive sampling revealed a few sheets of classical clear cell carcinoma together with a transitional zone in which both phases were intermingled. Five months after nephrectomy the patient died from pulmonary secondaries.

## Comment

In the largest studies of renal tumours (both from the Mayo Clinic) (Farrow *et al.*, 1968; Tomera *et al.*, 1983), the incidence of sarcomatoid renal carcinoma was 1.5 and 1% respectively. Of these, 3/37 patients (8%) and 0/13 (0%) showed osteogenic differentiation.

The origin of these tumours is debatable, but Macke *et al.* (1985) showed by electron microscopy that the spindle cells had epithelial characteristics and concluded that they originated from the malignant epithelial cells by a metaplastic process. The bone formation is also believed to be of metaplastic origin. A case of synchronous inde-

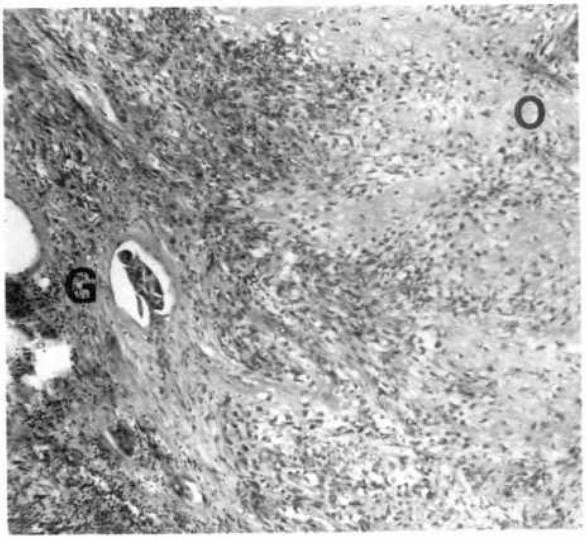

**Fig.** Sarcomatoid renal carcinoma showing a sarcomatous region with osteogenic differentiation (0) and a compressed, distorted glomerulus (G). (H and E × 100).

pendent primary osteosarcoma and adenocarcinoma of the kidney has been described by Moon *et al.* (1983) but no electron microscopy was performed to rule out metaplastic change. The prognosis of these tumours is very poor, with the tumour being stage 2 or worse at presentation in over 80% of cases. It is interesting to note that in the report by Bertoni *et al.* (1987), the 2 patients (of 19) who were alive 73 months post-operatively had less than 5% sarcomatoid metaplasia in their tumours.

### Acknowledgement

We thank Mr B. H. Walmsley for permission to report this case.

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Requests for reprints to: I. Sugarman, Department of Urology, St Mary's Hospital, Milton Road, Portsmouth PO3 6AD.

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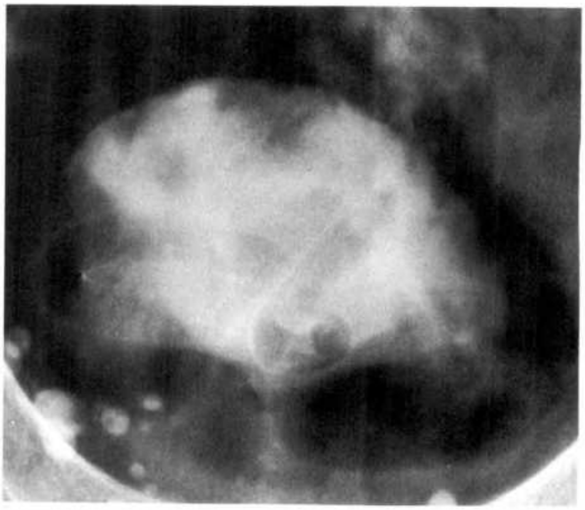
# Retained Catheter Tip Causing Recurrent Urinary Tract Infection in a 91-year-old Man

R. A. PERSAD, A. PAISLEY and P. J. SMITH, *Department of Urology, Royal Infirmary, Bristol*

Foreign bodies may find their way into the bladder by several routes: self-insertion, iatrogenically, accidentally or traumatically. In any of these instances their presence may go undetected for some time and presentation may eventually occur in the most unexpected manner.



## Case Report

A 91-year-old man was referred with a 3-year history of urgency and incontinence associated with repeated urinary tract infections. He had had a prostatectomy 4 years earlier and remembered being told that one night whilst in a confusional state after his operation he had pulled out his urethral catheter. This necessitated the reinsertion of a catheter without any further problems and he was discharged in due course. An intravenous urogram later showed what appeared to be a large "vermiform" foreign body (Fig.). He underwent cystoscopy at which a very calcified catheter tip was found lodged in the bladder near to the trigone. The foreign body was removed endoscopically and he has been well since.

## Comment

It is suggested that any catheter (either suprapubic or urethral) which has been inserted or removed with undue difficulty should be inspected carefully to ensure that it is intact when removed. Special attention should be paid to the catheter which has been pulled out by the confused or aggressive patient. In addition, patients who have persistent voiding dysfunction after prostatectomy should have a plain X-ray of their bladder, proceeding to endoscopy if no other cause is found for their symptoms.

Requests for reprints to: R. A. Persad, Department of Urology, Bristol Royal Infirmary, Bristol BS2 8HW.

# Intramural Vesical Abscess

K. K. SARKAR, T. PHILP and P. THURLEY, *Department of Urology, Whipps Cross Hospital, London*

## Case Report

A 60-year-old white male presented with a 2-month history of recurrent coliform urinary infections which had failed to respond to repeated courses of antibiotics. He complained of suprapubic discomfort and drenching night sweats with high fevers. Investigation showed a moderate leucocytosis and an ESR of 50. A urogram (Fig. 1) showed normal upper tracts but a smooth filling defect on the left side of the fundus of the bladder. On ultrasonography this appeared to be a thick-walled intramural abscess. At cystoscopy an elevated mass with inflamed overlying mucosa was seen on the left posterior wall of the bladder well above the ureteric orifices. A pericolic abscess or a necrotic tumour was suspected, but deep mucosal biopsies showed inflammatory changes only. A barium enema did show sigmoid diverticular disease but a CT scan confirmed that the lesion was confined to the bladder wall with no extravesical spread; the colon was quite separate (Fig. 2). The abscess cavity was deroofed by transurethral resection and pus was drained. The pus and tissue from the abscess wall were cultured and grew coliforms. Culture for acid-fast bacilli was negative and histology revealed only non-specific mucosal inflammation. Normal detrusor muscle was present in the abscess wall. Post-operatively all symptoms settled. Six months later, cystoscopy showed a well healed scar and otherwise normal bladder. A micturating cystogram showed no reflux or diverticula.

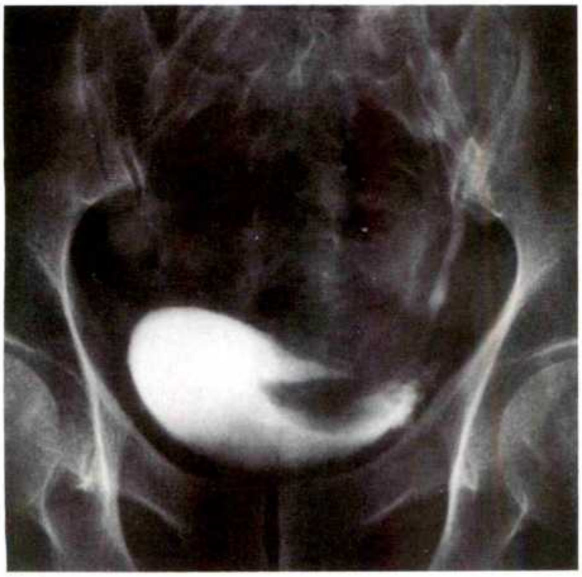


**Fig. 1** 10 min IVU film.

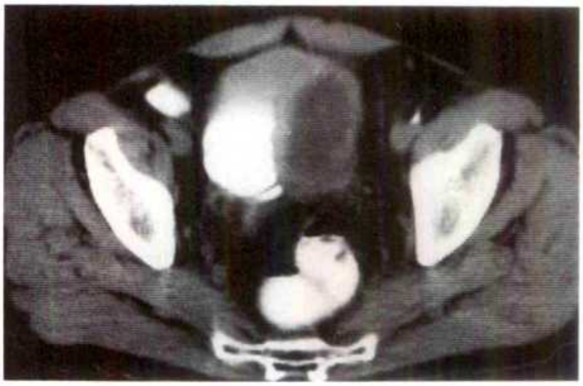


**Fig. 2** Transverse CT scan of bladder and pelvis.

## Comment

Vesical abscesses have rarely been reported and most are secondary to inflammatory bowel disease (Kapp *et al.*, 1985). An isolated intramural abscess secondary to a foreign body was reported by Nemeth and Kiss (1981). In our patient we were unable to identify any aetiological factors. Hutch diverticula, a walled-off saccule or a blind-ending bifid ureter were considered but excluded by investigation. The presence of coliform organisms makes it likely that the abscess resulted from an ascending urinary tract infection. This appears to be the first description of a simple pyogenic abscess in the wall of the bladder.

## References

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Requests for reprints to: K. K. Sarkar, Department of Urology, Whipps Cross Hospital, Leytonstone, London E11 1NR.

*British Journal of Urology* (1990), **66**, 666–667
0007/1331/90/0066–0666/$10.00

# Points of Technique

## Reduction of Paraphimosis

T. C. WATERS and V. SRIPATHI, *Department of Surgery, Princess Margaret Hospital for Children, Perth, Australia*

The accepted treatments of paraphimosis include simple reduction or dorsal slit (Klauber and Sant, 1985). A dorsal slit necessitates circumcision at a later date. Although many parents are happy for their sons to be circumcised, a significant number prefer the prepuce to be left intact. This is where primary reduction plays an important role.

### Technique

Paraphimosis is always associated with varying degrees of oedema of the prepuce, which may make reduction difficult. In our experience, it has been advantageous to make multiple stabs in the oedematous area with a 25 gauge hypodermic needle and then firmly but gently squeeze out the oedema fluid. This enables the prepuce to be easily drawn over the glans. Even "irreducible" paraphimoses can be reduced using this technique, allowing the child to undergo an elective circumcision at a later date, if the parents so desire. One such patient presented with a paraphimosis of 7 days duration. This had been treated as balanitis by the Local Medical Officer. There was severe oedema and angulation of the penis with a maximum diameter of 8 cm. Nevertheless, this technique allowed easy reduction. In older children, puncture and reduction can be done as an out-patient procedure using a penile ring block with a local anaesthetic. No secondary infection or other complication has been seen to date in 8 children in whom it has been attempted at this hospital. We believe that it has a definite role in the treatment of paraphimosis.

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Requests for reprints to: T. C. Waters, 110A Victoria Avenue, Dalkeith, Western Australia 6009.

## Easy Localisation of Stones on Ultrasound Monitored Lithotriptors

J. TALATI, *Department of Surgery (Urology), The Aga Khan University, Karachi, Pakistan*

Ultrasound localisation of stones is often erroneously thought to be difficult. In order to facilitate stone localisation, the Dornier MPL 9000 lithotriptor has a light pen localisation system. The kidney is visualised on the monitor and the stone touched with a light pen. An auto-positioning (autopos) device then automatically moves the patient so that the stone lies at the focus point of the shockwave. At times, the patient is so far off target initially that the autopos limits are reached before bringing the stone into the focal point.

We have bypassed the need for autopos. Looking at the plain abdominal X-ray, the surface marking of the stone is worked out as "x" finger breadths medial to the tip of the last palpable rib and "y" finger breadths vertically down from that point. This is surface marked on the patient's back by a marker. An ultrasound mobile arm can be used to check that the stone lies immediately deep to this point.

The patient is so positioned on the water cushion that when he lies down, the marked point lies over the centre of the ellipsoid (Fig.). Very minor adjustments in the longitudinal transverse and vertical axes are then made for accurate targeting.

Positioning time varies from 2 min to 1.5 h during one treatment. Most patients (80%) are

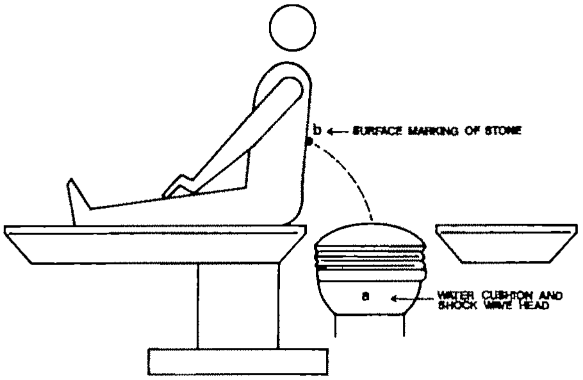
b ← SURFACE MARKING OF STONE
a ← WATER CUSHION AND SHOCK WAVE HEAD

**Fig.** Patient correctly positioned so that when he lies down, the stone will lie above the focus point.

positioned within 10 min. Difficult positioning manoeuvres that are necessary in obese patients still require patience and repeated adjustments.

The technique described will facilitate rapid localisation.

Requests for reprints to: J. Talati, Department of Surgery (Urology), The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi-74800, Pakistan.

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# Safer Nephroureterectomy in the Treatment of Transitional Cell Carcinoma of the Upper Urinary Tract

P. PERIMENIS and G. BARBALIAS, *Department of Urology, University of Patras, Patras, Greece*

Tumours of the renal pelvis and ureter account for approximately 2% of genitourinary malignancies (Johnson *et al.*, 1988). Newman *et al.* (1967) suggested that nephroureterectomy, with a cuff of bladder, is the most effective treatment. Special care must be taken to minimise recurrences due to the spread of cancer cells within the wound (Novick and Stewart, 1976).

## Technique

Three men underwent nephroureterectomy over a 12-month period. Two had cancer in the renal pelvis and 1 in the lower ureter. All had positive cytology.

Urine was collected for cytological examination and the ureteric orifice on the side of the lesion was coagulated transurethrally. The bladder was washed out with distilled water and then filled with the same fluid until it could be opened following nephrectomy. The bladder was then emptied, washed out once more, and this sample was sent for cytological examination. The ureter was removed with the surrounding bladder wall.

One year post-operatively the patients remain free of recurrences.

## References

**Johnson, E. D., Swanson, A. D. and von Eschenbach, C. A.** (1988). Tumors of the genitourinary tract. In *Smith's General Urology*, ed. Tanagho, E. A. and McAnich, J. W. Chapter 19, pp. 330–421. Connecticut: Appleton and Lange.

**Newman, D. M., Lawrence, E. A., Wishard, W. N. *et al.*** (1967). Transitional cell carcinoma of the upper urinary tract. *J. Urol.*, **98**, 322–327.

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Requests for reprints to: P. Perimenis, 42 Nafpactou Street, GR 26331 Patras, Greece.

*British Journal of Urology* (1990), **66**, 668
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0007-1331/90/0066-0668/$10.00

# Correspondence

Dear Sir,

*re* **Elevation of the vagina during colposuspension: the use of Deaver retractor.** B. T. Haylen *et al. Br. J. Urol.*, **63**, 220, 1989.

*Letter to the Editor.* I read with interest the 'Point of Technique' describing the advantages of using a Deaver retractor during colposuspension. I agree entirely. Our experience with this technique in 174 patients undergoing colposuspension for stress incontinence was reported recently (A. Korda *et al. Aust. N.J. J. Obstet. Gynaecol.*, **29**, 146–149, 1989).

Yours faithfully,

A. Korda
Department of Obstetrics and Gynaecology, Royal Prince Alfred Hospital, Sydney, Australia.

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Dear Sir,

*re* **Endoscopic transvesical extramural ureterolithotomy.** S. N. Lloyd and C. Kennedy. *Br. J. Urol.*, **65**, 326–328, 1990.

The authors describe an ingenious and remarkable technique for the management of calculi impacted in the lower ureter.

In their discussion of alternative approaches to calculi impacted in the lower ureter they mention, among other options, the transvaginal approach and state that it was "first described by Emmet in 1879". The transvaginal approach, which is a true short cut to the lower ureter, is actually a very elegant, expedient, safe, technically easy, highly successful and almost forgotten old surgical route to remove calculi from the lower ureter; it is a route which is especially useful in pregnant women (F. S. Haddad. *Urology*, **21**, 211, 1983). It was used and described almost 1000 years ago in a famous book on surgery written by Albucasis (d. 1013 AD). Albucasis' real name was "abuw alqȧAsim alzahrȧAwiŷ". He lived in "alzahrȧA", which was related to Cordova ("the ornament of the world") as Versailles was destined to become related to Paris. The thirtieth volume of his encyclopaedic work was dedicated to all branches of surgery, including urology, and contained over 200 illustrations of surgical instruments with a description of their usage; many were designed by Albucasis himself; this remarkable book was translated into Latin by Gerard of Cremona (1114–1187). Between 1497 and 1544, a period of less than 50 years, it had at least 10 Latin editions. It served as the main source of surgical knowledge for the early European surgeons, including Roger of Salerno, Salicetti, Lanfranchi, Henry of Mondeville, Mondinus of Bologna, Bruno of Calabria, Guy of Chauliac, Valescus of Taranta, Hans of Gersdorff, Fabricius of Aquapendente and many others, all of whom quoted from Albucasis' work. The book was still in use in the eighteenth century; John Channing of Oxford published, in 1778, the Arabic text as well as a Latin translation. Its Arabic text was republished recently with a superb English translation (M. S. Spink and G. L. Lewis. (1973). *Albucasis on Surgery and Instruments.* Berkeley: University of California).

Alcucasis writes in Chapter 61 (volume 30), which is entitled "The extraction of stones from women . . .": ". . . Order the midwife to introduce her finger in the patient's vagina and look for the stone after she places her left hand on the bladder and squeezes forcefully. If she finds the stone, she should milk it downwards as much as possible . . . she should then cut on it in mid vagina introduced into the small incision; if the stone is felt, the incision should be enlarged until the stone is extracted."

Albucasis has to his credit several other contributions to urology and surgery. He was most certainly the greatest surgeon of his time and the greatest Arab surgeon of all times; he deserves to be remembered.

Yours faithfully,

Farid S. Haddad
Chief of Urology, Carl T. Hayden Veterans Administration Medical Center, Phoenix, Arizona, USA.

*British Journal of Urology* (1990), **66**, 669–670

# Notices

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

Abstracts of contributions to be considered as either papers, posters of videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 4 January 1991.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

## Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

## Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

## Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

## Norwich Eaton Travelling Scholarship

The scholarship(s) will cover travel, accommodation and registration expenses associated with attending the Society of University Urological Residents and American Urological Association meetings. They will be awarded annually until such time as either the Senior Urological Registrars Group or Norwich Eaton Ltd decide not to continue and will be available to any person appointed to an accredited urological training post.

The scholarship(s) will be awarded to the person(s) presenting the winning paper at the Senior Urological Registrars Group Annual Meeting. The winning paper(s) will be selected by those members of the Senior Urological Registrars Group present at the meeting and appointed to urological training posts.

### BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000.00 for any article(s) of outstanding merit published each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to urological centres outside Britain for consideration by the adjudicators, who shall be the Chairman of the Editorial Board, the Honorary Editorial Secretary and one nominee from Council. This prize is not necessarily awarded annually.

## Prizes and Awards

### British Association of Urological Surgeons

**President:** Mr. R. T. Turner-Warwick, DSc, DM, MCh, FRCS, FACS.

*Annual Meeting: Scarborough. 10–13 July 1990*

### St Peter's Medal

At the Annual Dinner the President presented the St Peter's Medal to Mr D. G. Thomas, FRCS, after a citation given by Mr J. L. Williams, FRCS.

### St Paul's Medal

At the Annual Dinner the President presented the St Paul's Medal to Professor R. Hohenfellner, MD, after a citation given by Professor J. M. Fitzpatrick.

### BAUS Travelling Fellowship

The 1990 prize was awarded to Diane E. Nurse for her contributions to Volumes 63 and 64, 1989.

### DANTEC Urology Prize

The award for 1989 was given to Mr. I. Eardley for the paper entitled "The value of urethral sphincter electromyography in the differential diagnosis of Parkinsonism", *British Journal of Urology*, **64**, 360–362.

### Surgitek Prize

The 1990 Surgitek Prize was awarded to Mr D. P. S. Sandhu for his paper entitled "Increased survival of patients with massive lymphadenopathy and prostrate cancer".

### Simpla Prize

The 1990 prize was awarded to Messrs S. Carter, S. Patel and J. Ramsay for their project entitled "24-hour home monitoring of urinary performance".

### Bard Silver Medal

The award for 1990 was given to Mr S. Prescott, Western General Hospital, Edinburgh, for his essay entitled "Empiricism of mechanism: the use of BCG for bladder cancer".

### Norwich Eaton Travelling Fellowship

The Fellowships were awarded to Mr M. G. Lucas, Edinburgh, for his paper entitled "They do like it up 'em!" and to Mr J. Anderson, Sheffield, for his paper entitled "A urodynamic approach to the management of postoperative urinary retention".

*British Journal of Urology* (1990), **66**, 671–672

# Diary

1991

| | |
|---|---|
| January 4 | Final date for submission of abstracts for 1991 BAUS Annual Meeting. |
| January 14–February 1 | Short Courses in Urology and Nephrology including: Disorders of Bladder Function, Reconstructive Surgery, Disorders of the Female Urinary Tract, Urological Trauma and Emergencies, Acute and Chronic Renal Failure, Transplantation, Management of Stones and Upper Tract Obstruction, Endoscopic Urology and Recent Technological Advances in Urology, The Retroperitoneum, Surgical Techniques, Urological Problems in the Elderly. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| January 22–25 | Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark. |
| February 3–6 | International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India. |
| February 7–8 | Uro-Radiology '91. For further details of this course please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| February 23–March 2 | Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ. |
| March 11–15 | Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| March 16–17 | International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 8–28 | Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 12–13 | Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France. |

| | |
|---|---|
| April 14–19 | Forty-fourth Annual Scientific Meeting of the Urological Society of Australasia, Sheraton Mirage Hotel, Gold Coast, Queensland, Australia. Contact: G. Holmes, President, Brisbane Urology Clinic, 11th Floor, 149 Wickham Terrace, Brisbane, QLD 4000. |
| May 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi–Belgium. |
| June 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| June 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |
| June 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
| July 2–3 | Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllõi ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |
| 1992 | |
| January 10 | Final date for submission of abstracts for the 1992 BAUS Annual Meeting. |
| May 10–14 | American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC. |
| June 21–26 | BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office. |

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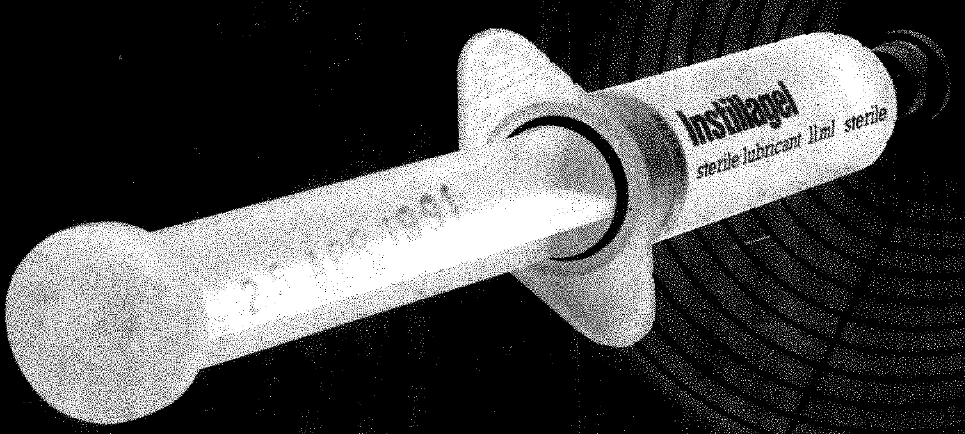
The sterile lubricant for urethral catheters and instruments



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| Methyl p-hydroxybenzoate, BP | 0.060 g |
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| Gel | ad 100.000 g |

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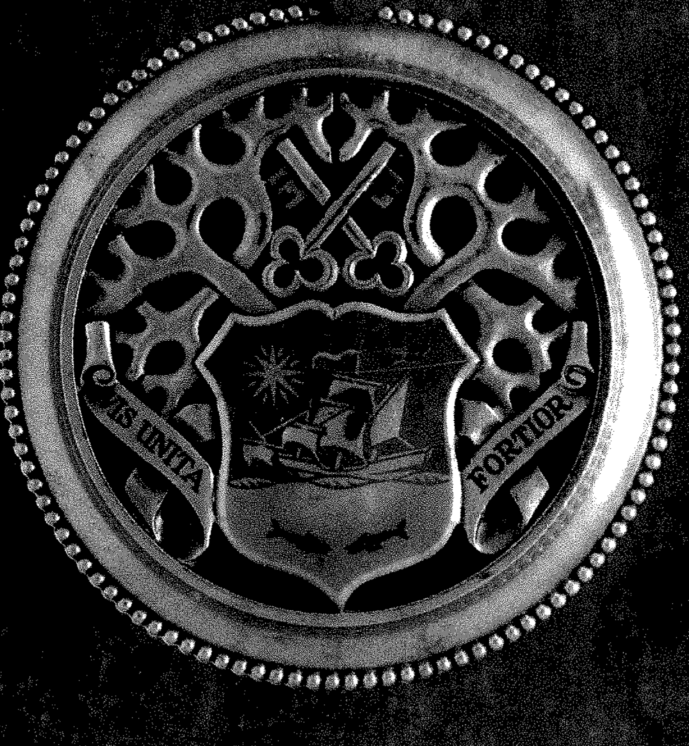

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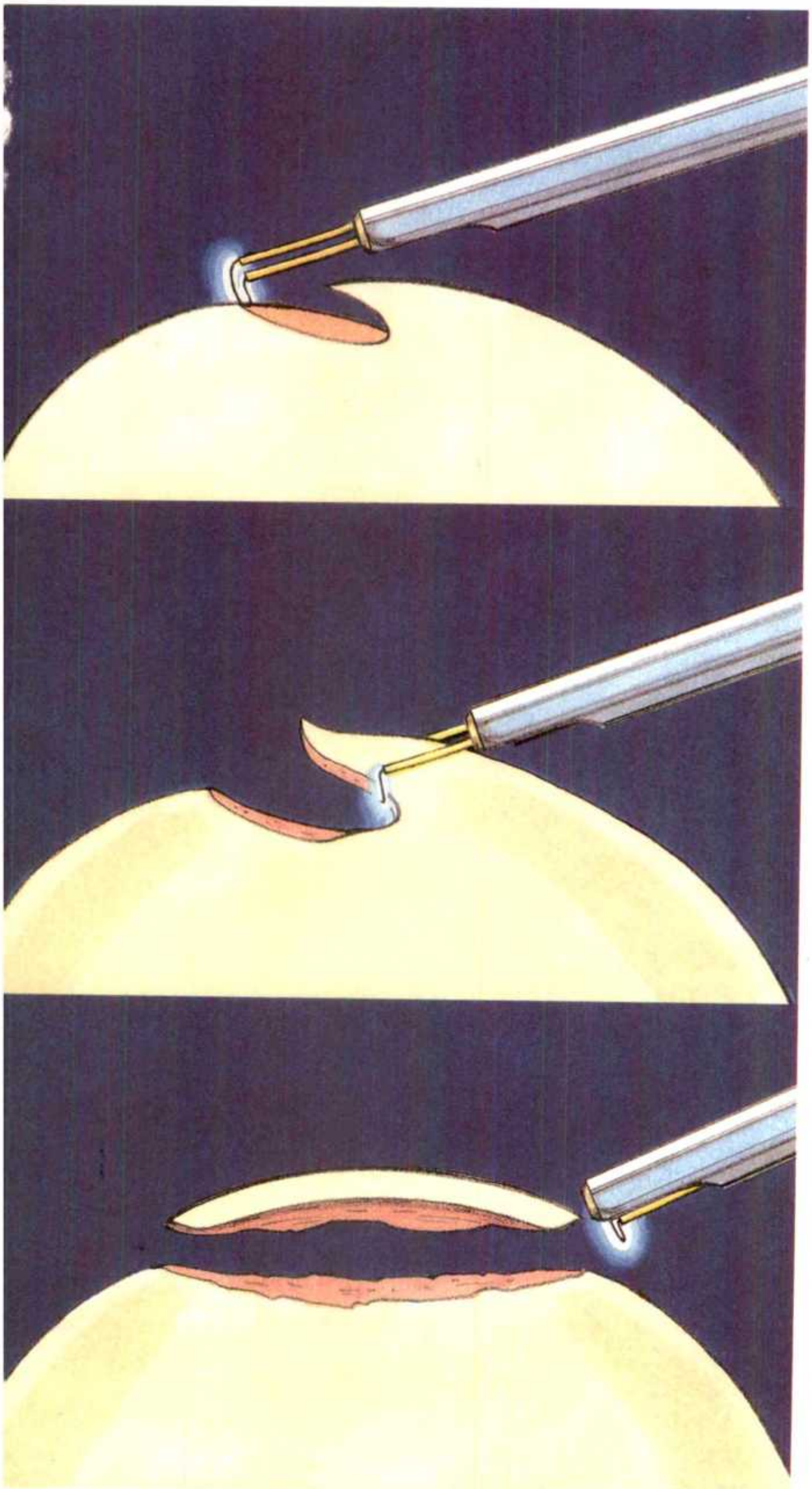
# THE NEW TD411-RS: FOR THE CUTTING EDGE IN ELECTROSURGICAL PERFORMANCE.



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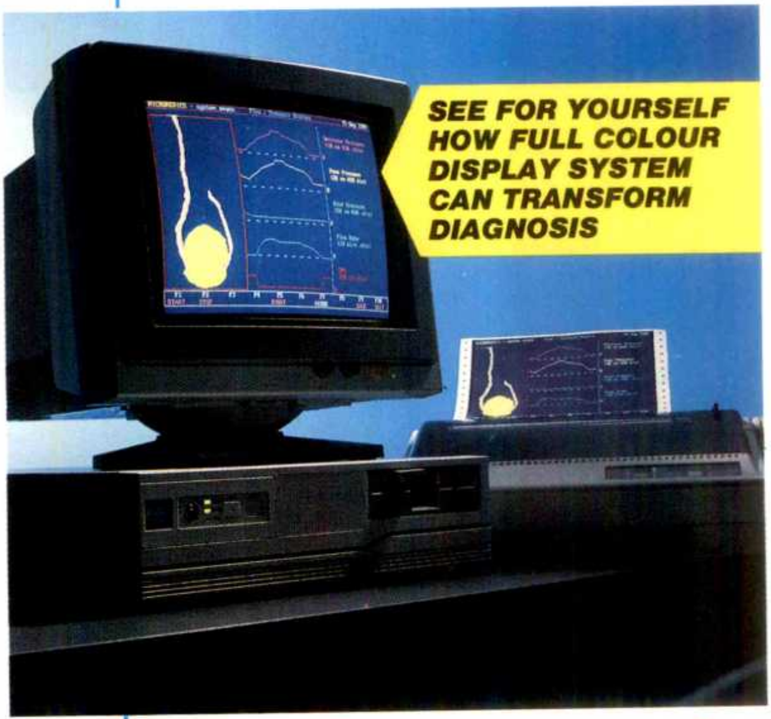
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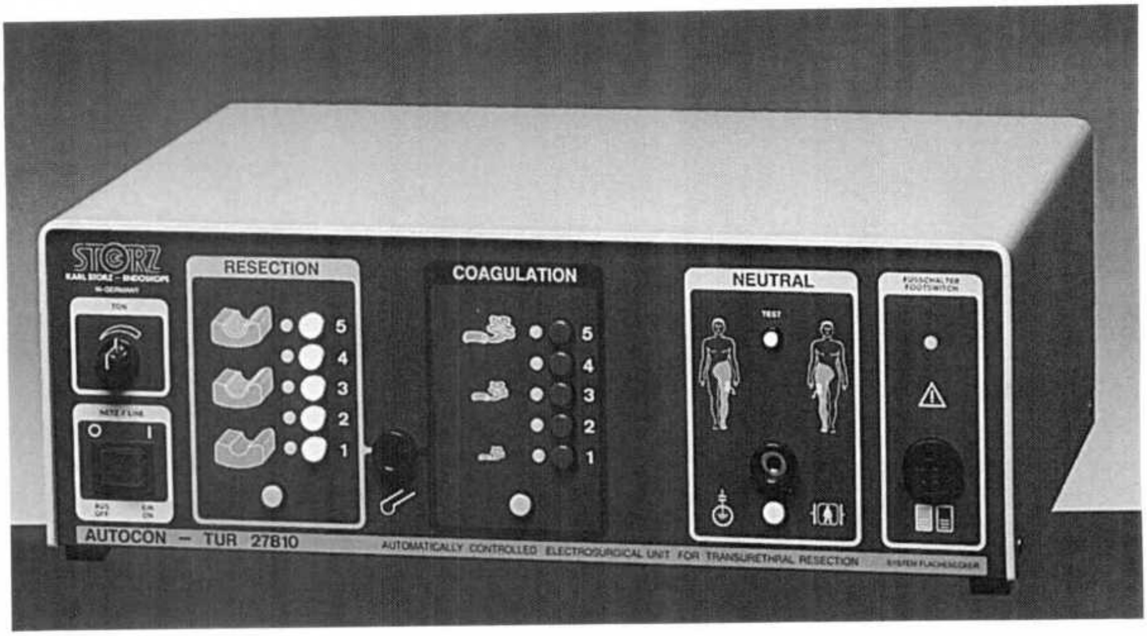

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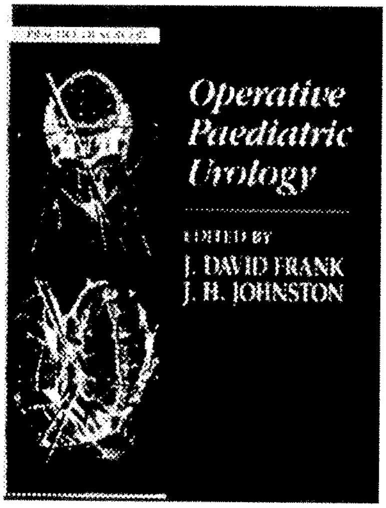

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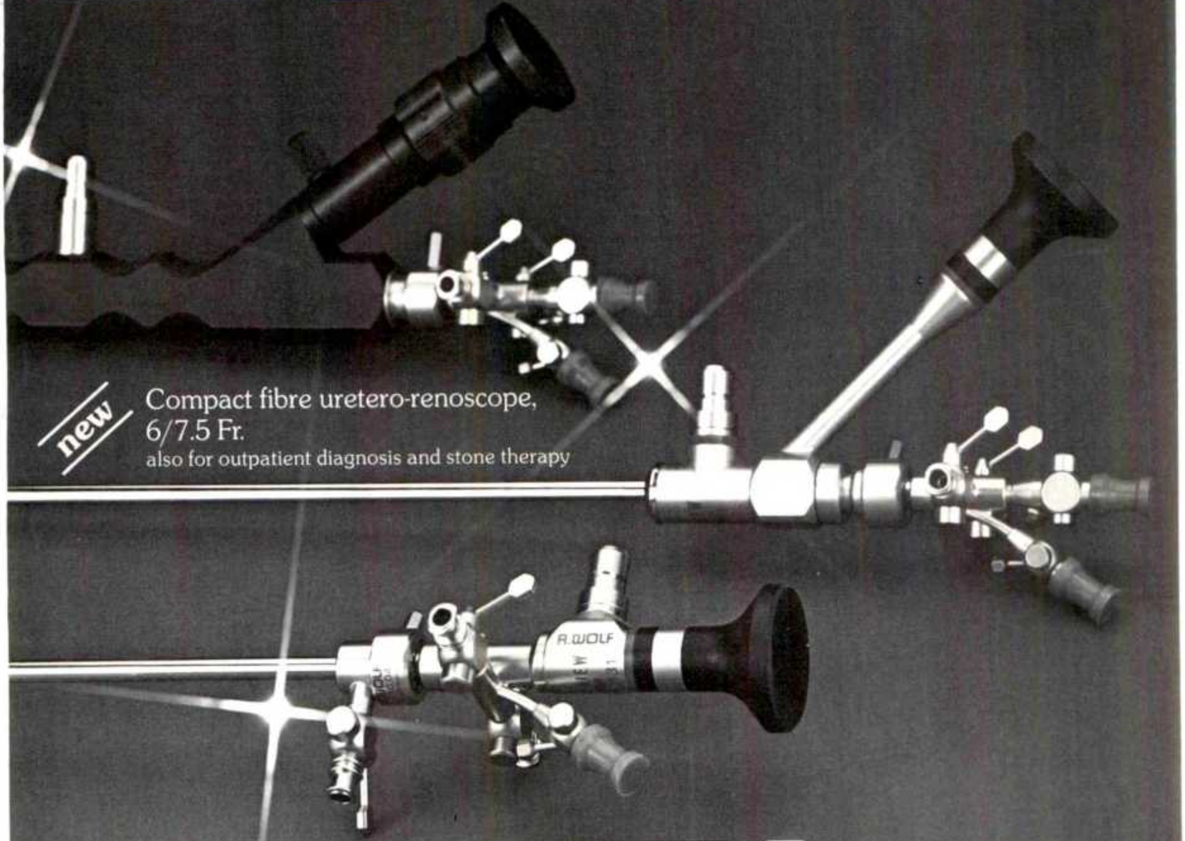

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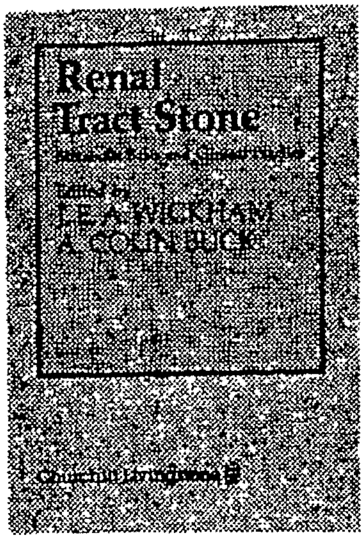

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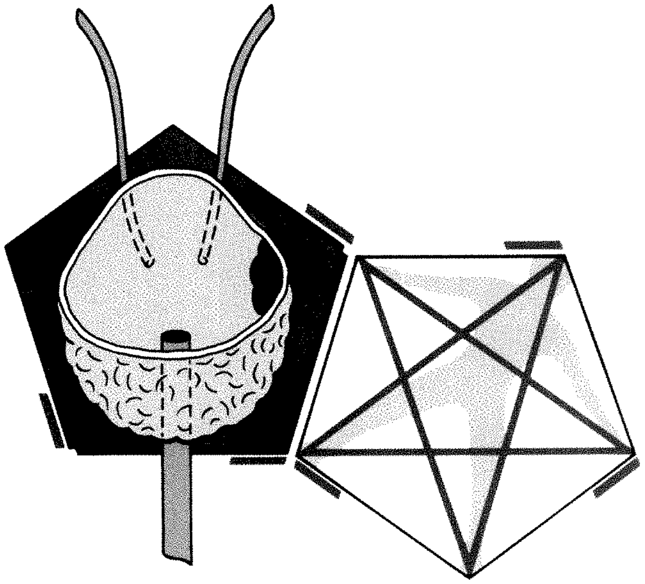

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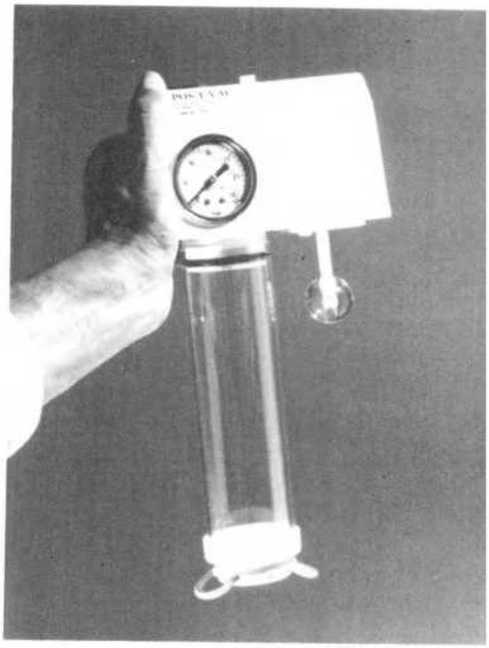

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REVIEW

# Prostatic Specific Antigen

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In 1979, Wang *et al.* reported the isolation and purification of an antigen from prostatic tissue which was both organ-specific and distinct from prostatic-specific acid phosphatase and to which they gave the name of prostate-specific antigen (PSA). It is a glycoprotein with a molecular weight of 33,000 and has been identified as occurring in the cytoplasm of prostatic epithelial cells comprising the prostatic ductal elements (Papsidero *et al.*, 1981).

PSA was first identified in the serum of men with prostatic cancer in 1980 (Papsidero *et al.*, 1980) and this led to the suggestion that measurement of the level of circulating PSA can be used for screening, diagnosis, staging, prognosis, assessment of response to treatment and prediction of relapse in patients with prostatic cancer.

PSA has often been evaluated not as a test in its own right, but in comparison with prostatic acid phosphatase (PAP). The status of PAP was reviewed by Pontes (1983) and Holle (1987). The former also includes a summary of the position of PSA at that time.

PSA estimation is time-consuming, labour intensive and expensive: the cost of consumables alone of the 2 widely available commercial packs is about £5 for one (Tandem-R PSA: Hybritech) and £3 for the other (Pros-Check PSA: Yang Laboratories Inc.). Enzymatic PAP costs less than £1 per test. At the Royal Marsden Hospital, the introduction of PSA testing produced identifiable additional costs of £5000 in 9 months. However, PSA may enable a significant reduction in other costly investigations currently widely used in the management of patients with prostatic cancer.

## Immunocytochemical Techniques in Tissue and Bone Marrow

The use of immunohistochemical techniques with antibodies to PSA has facilitated the identification of the site of origin of tumours difficult to identify by conventional histological methods (Lemberger *et al.* 1984; Ford *et al.*, 1985). The specificity and sensitivity of PSA in these circumstances approaches 100% (Lemberger *et al.*, 1984), although it is only in a small proportion of cases that it is necessary.

A further extension of PSA staining by immunocytochemical techniques was described by Mansi *et al.* (1988). In a small series of patients with prostatic cancer, cells staining with PSA were identified in the bone marrow of 2 of 15 patients with no metastases on conventional staging, and in 11 of 15 with metastatic disease. It is therefore possible that staining bone marrow samples with antibodies to PSA may prove a useful adjunct to conventional staging techniques, and further validation of the technique is needed.

## Normal Values and Decision Values

A possible area of confusion in interpreting the published results of PSA testing lies in the fact that the 2 commercially available kits use different methodologies and their results are not directly comparable. Pros-Check PSA is a competitive radioimmunoassay in which displacement of radiolabelled PSA from a polyclonal antiserum is measured and produces values 1.5 to 1.8 times higher than the solid-phase immunoradiometric "sandwich-type" assay of Tandem-R PSA (Chan *et al.*, 1987; Hortin *et al.*, 1988). The differential

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between the 2 methods is not constant and varies with the amount of antigen present. There is no constant standard or, at the present time, a central reference laboratory for quality control. Comparisons between results produced in different laboratories should therefore be made only with great caution. It may be an over-simplification to suggest that the Pros-Check technique is less specific than Tandem-R, but the higher values obtained and its use of a polyclonal rather than a monoclonal antibody lead to this conclusion. PSA is detectable in the serum of women, albeit in small values (Morote *et al.*, 1986) and it is presumably therefore not truly specific however measured.

There is widespread agreement that in men under 40 and in women, PSA values greater than 4 ng/ml are not seen, and this value has therefore been taken as the upper limit of normal. In men of the prostatic cancer age group, however, there is wider variation. Morote *et al.* (1986) found levels of >10 ng/ml in more than 50% of men with "complicated" BPH (patients with acute retention and indwelling catheters) and levels of >4 ng/ml in over a third of men with uncomplicated BPH. Ferro *et al.* (1987) found that 32.5% of men with BPH had PSA levels above 10 ng/ml. Stamey *et al.* (1987) found an increase in PSA of 0.3 ng/ml/G in BPH. Prostatitis is associated with higher PSA values than uncomplicated BPH or normal prostates (Morote *et al.*, 1986; Brawer *et al.*, 1989).

The search for absolute normal values is misguided. Rock *et al.* (1987) used different values to make clinical decisions depending upon the stage and point in the natural history of their patients and therefore employed the concept of decision values rather than absolute definitions of normality and abnormality.

The effects of prostatic surgery and prostatic massage have been debated. Stamey *et al.* (1987) found that prostatic massage increased PSA by a factor of 1.5–2 and a 4-fold increase after cystoscopy, results similar to the "complicated BPH" patients of Morote *et al.* (1986), and a marked rise after needle biopsy. Stamey *et al.* (1987) and Vesey *et al.* (1988) observed that TUR of benign prostates also produced a marked (50–60 fold) rise of PSA, though the elevation was much less after TUR in malignant disease.

It would seem wise, therefore, to avoid estimating PSA until any effects of prostatic manipulations have ended. With a half-life of 2.2 to 3.5 days (Stamey *et al.*, 1987; Oesterling *et al.*, 1988) how long a time interval should be left will depend upon the extent of the procedure performed.

### Selectivity, Sensitivity and Predictive Value

The importance of sensitivity and specificity in the elevation of a biochemical test is well understood. The sensitivity of PSA is the percentage of patients with prostatic cancer whose PSA values exceed the decision value, and the specificity is the percentage of patients without cancer whose PSA values are less than or equal to the decision value. The predictive value of a test is proportional also to the prevalence of the condition sought in the population tested. Positive accuracy is the proportion of people in the tested population with a "true" positive value and negative accuracy the proportion with a "true" negative value (Feinstein, 1977). The algebraic calculation by which these figures are reached is:

$$\text{Positive accuracy} = \frac{sP}{sP + (1-f)(1-P)}$$

$$\text{Negative accuracy} = \frac{f(1-P)}{f(1-P) + (1-s)P}$$

where $P$ = Prevalence
$S$ = Sensitivity
$f$ = Specificity

### Screening

If PSA testing is to be used for the detection of latent (T0) prostatic carcinoma, there must be sufficient negative accuracy to be sure that patients are not being missed by false negative results and sufficient positive accuracy for the time and expense of setting up a screening programme to be productive. Cumulated data from the literature suggest a positive accuracy of 10% at a decision value of 4 ng/ml and 9% at a decision value of 10 ng/ml. The negative accuracies are 98 and 95% respectively. The prevalence of T0 carcinoma in these reports is, however, low (4–5%).

The incidence of T0 prostatic cancer in males over 50 years old is 20 to 25% (Breslow *et al.*, 1977). If a conservative estimate of the true prevalence of prostatic cancer of 10% is taken, the positive accuracy of PSA rises to 21%, with a negative accuracy of 91% (decision value 4 ng/ml) and if it is assumed that the incidence is 25%, the positive accuracy rises to 45% without significantly reducing negative accuracy (89%). Although this still means that 55% of patients with values >4 ng/ml will not have prostatic cancer, and therefore does not suggest that PSA alone could be used as a screening test, it is arguable that in conjunction with other diagnostic methods, *e.g.* trans-rectal prostatic ultrasound (TRUS), a feasible programme for screening could be devised.

### Diagnosis

The only diagnostic criterion for prostatic cancer is biopsy, and no serum marker can take the place of histological diagnosis. An elevated PSA level could allow urologists to expedite the admission of patients who potentially have cancer (Armitage *et al.*, 1988; Powell *et al.*, 1989). This has obvious attractions in units with long waiting lists for prostatic surgery. If the prevalence of clinically undetected carcinoma in a group of patients with prostatic symptoms is 10%, the negative accuracy of a PSA value of >10 ng/ml is 94% and the positive accuracy 35%. If all patients with a PSA >10 ng/ml are expedited, few will linger with an undetected tumour, although two-thirds of them will not have cancer. It is for individual clinicians to decide whether to employ this method of giving priority in the light of local circumstances.

PSA assay is of considerable value in assessing the patient so frequently seen by the urologist: the frail old man with multiple pathology who just might have a prostatic carcinoma. Prostatic cancer of any clinical significance is very unlikely if PSA is <20 ng/ml and further unnecessary investigation can be avoided.

### Staging

Radio-isotopic bone scintigraphy has until now been the investigation of choice in determining the metastatic status of patients with prostatic cancer (O'Donoghue *et al.*, 1978; Hetherington *et al.*, 1987). The negative accuracy of PSA level of 20 ng/ml is 92% and therefore patients with PSA levels of 20 or less can be assumed to have no metastases and do not need bone scans. The positive accuracy is 63% and therefore more than a third of patients with a PSA >20 ng/ml will not have metastases.

Stamey and Kabalin (1989) and Brawer *et al.* (1989) found increasing PSA levels with higher grade tumours and a direct correlation between prostate volume and PSA. PSA >20 ng/ml in a patient with a small well differentiated tumour is more likely to indicate metastatic disease than a higher level in a patient with a bulky, poorly differentiated tumour. In a series at the Royal Marsden Hospital, PSA levels up to 80 ng/ml in patients with extensive T3M0 tumours were found (unpublished data). Bone scanning is therefore still necessary in patients with PSA >20 ng/ml.

The ability of PSA to detect capsular invasion in M0 patients is important in those units where total prostatectomy is undertaken. The positive accuracy rate for a decision value of 10 ng/ml is 70% and the negative accuracy 74%; 30% of patients will be overstaged and 25% understaged by PSA. It is inferior to TRUS in identifying extra-capsular invasion, though where TRUS is not available PSA represents a valuable staging test.

Lymphatic invasion is particularly difficult to identify by any means short of lymph node biopsy. Both CT scanning and bipedal lymphangiography have a false negative rate of 30 to 40%. Stamey *et al.* (1989a) in a series of 102 patients found a positive accuracy rate of 68% and negative accuracy of 79%, though the prevalence of lymph node metastases in their patients was low (12.7%) (decision value 20 ng/ml). If the prevalence of lymph node involvement in M0 patients is 40%, a PSA value of 20 ng/ml has a positive and negative accuracy of approximately 80%, comparable to radiological imaging. It is therefore reasonable to suggest that the complex and expensive radiological tests should be reserved for those patients with a PSA of <20 ng/ml in whom radiotherapy or radical surgery is being considered.

### Prognosis

The level of circulating PSA is directly proportional to prostatic volume and grade (Stamey *et al.*, 1989b). It is therefore logical to conclude that prognosis is equally strongly related to PSA (Killian *et al.*, 1985). However, PSA estimation is only 1 of a number of prognostic measurements. Non-specific indicators (alkaline phosphatase, haemoglobin and weight loss) are often the best providers of prognostic guidance.

### Response to Treatment

PSA levels in localised prostatic carcinoma treated by prostatectomy fall in relation to its half-life in serum and the level of circulating PSA following operation can be calculated using an algebraic formula described by Oesterling *et al.* (1988). Stamey *et al.* (1989b) considered that any detectable PSA 3 weeks or more after prostatectomy indicated residual cancer even in the absence of any other indicator, but they produced no evidence in support of this contention and further evaluation is necessary before their view can be widely accepted.

PSA remains detectable after radiotherapy in most patients, though with declining values for up to a year. Interpretation of serum PSA levels in irradiated patients needs caution: patients who develop metastases after radiotherapy may have PSA levels significantly lower than those of untreated patients with metastases (Stamey *et al.*, 1989b). Serial PSA estimations are of the greatest use: increasing values are likely to precede clinically evident metastases, though the numbers documented are small and further study is needed.

In patients treated with androgen deprivation, there is usually a rapid fall of PSA to <4 ng/ml, though there is no quantitative correlation between change in PSA and reduction in prostate volume (unpublished data). Failure of PSA to fall to these levels within 3 to 6 months is associated with poor prognosis (Siddall *et al.*, 1986).

## Prediction of Relapse

Many patients are managed by surveillance only. The potential risks of this policy are well recognised but in untreated patients serum PSA is a reliable indicator of tumour load (Stamey and Kabalin, 1989). Regular estimation of PSA in these patients will identify those with progressive disease and thus reduce the risk of unrecognised serious complications such as spinal cord compression or ureteric obstruction.

A single observation of an elevated PSA level in a treated patient cannot be taken as a reliable predictor of relapse, although there is evidence that a rise in PSA will precede other indications of disease progression by as much as 12 months. Regular serial PSA estimations should be undertaken in all untreated patients. The patient with elevated or rising levels needs closer surveillance than the patient with a low stable PSA. Routine bone scans in asymptomatic patients are not necessary.

PSA should be the first investigation in the patient with prostatic cancer who develops back pain or other symptoms. A PSA of <20 ng/ml in such a patient makes it unlikely that his cancer is the cause of his problem and obviates the need for further prostatic investigation.

## Conclusions

1. PSA testing should be a component part of screening for prostatic cancer.
2. Patients with prostatism and PSA >10 ng/ml should be given priority on a waiting list.
3. Patients with histologically confirmed prostatic carcinoma and PSA <20 ng/ml do not need staging bone scanning.
4. Patients with histologically confirmed prostatic carcinoma, PSA >20 ng/ml and negative bone scan can be assumed to have invasive disease and/or lymphatic deposits.
5. In treated patients, PSA provides an indication of response to treatment and prediction of relapse.
6. In treated patients, whether previous treatment was local or systemic, PSA is not as sensitive as in untreated patients.
7. In patients managed by surveillance, PSA is a valuable marker and allows identification of asymptomatic progression.
8. PSA can replace other investigations in the routine follow-up of patients with prostatic cancer.

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# Mobile Extracorporeal Shockwave Lithotripsy

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Summary—During the last 18 months, extracorporeal shockwave lithotripsy (ESWL) has been provided at Epsom District Hospital using a mobile unit containing a Dornier HM4 lithotriptor. Patients with upper ureteric and renal stones were selected for treatment, which was performed without anaesthesia or sedation as a day-case procedure; 83 patients were treated, 5 of them with bilateral stones. Seventy patients required 1 treatment session, 17 required 2 and 1 patient required 3. There were no serious complications but 3 patients needed ureteroscopy to remove obstructing stones. The overall success rate was 86%. The cost to treat each NHS patient was £253.

Mobile lithotripsy as a day-case procedure is a safe and cost-effective means of treating urolithiasis and can be performed in a District General Hospital.

In the last decade, ESWL has become established as the optimal treatment of most symptomatic renal and upper ureteric calculi (Eisenberger *et al.*, 1985). In the United Kingdom, financial constraints have limited the number of lithotriptors, leading to geographical inconvenience for patients and long waiting lists for treatment. The development of second and third generation lithotriptors has allowed transportation of the equipment as the waterbath used by the original Dornier HM3 is no longer necessary. Another advantage of current lithotriptors is that modification of the shockwave focus (HM4) or the use of alternative forms of energy for stone fragmentation permits treatment without anaesthesia.

At this hospital we have been treating patients with suitable renal and upper ureteric stones as day cases using a mobile lithotriptor leased by the hospital on a sessional basis. We report our experience of this form of therapy during the last 18 months.

## Patients and Methods

Patients presenting with renal or upper ureteric stones were assessed by excretory urography. Those whose stones were considered suitable for ESWL were offered treatment as a day-case procedure. Patients with renal stones >2 cm in diameter had an indwelling ureteric double pigtail stent (Cook Urological) inserted 24 h before treatment. In patients with ureteric stones an attempt was made to manipulate the stone into the kidney. If the attempt was successful, a pigtail stent was inserted to prevent downward migration of the stone before ESWL could be performed. If the stone could not be persuaded back into the kidney, an indwelling stent was passed and the stone treated *in situ*.

On the day of treatment, the patient was admitted to the day-case ward. A plain X-ray was obtained, trimethoprim 200 mg was administered orally and the patient was escorted to the lithotriptor unit. If undue pain was experienced during treatment, pithedine was administered intravenously. Following treatment the patient walked back to the ward and was allowed home between 1 and 2 h later. Trimethoprim was administered for a further 4 days and patients were instructed to contact the hospital if they developed a temperature, severe pain or nausea. Patients were seen and X-rayed in the out-patient clinic 4 days, 4 weeks and 4 months after ESWL.

The lithotriptors used were the Dornier HM4 (10 visits) and the Dornier MPL 9000 (2 visits). Both

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use underwater spark gap shockwave generators. The HM4 uses fluoroscopic localisation and the MPL 9000 uses ultrasound localisation, allowing treatment of radiolucent stones and gallstones.

## Results

In all, 83 patients were treated, 5 with bilateral stones, making 88 renal units treated. Table 1 shows the location of the stones and the number of patients with stents.

A total of 70 patients received 1 treatment, 17 received 2 treatments and 1 patient who had percutaneous debulking of a staghorn calculus required 3 sessions. The average number of shockwaves per session was 2100 (range 1000–2600). Four patients needed intravenous pethidine (all had ureteric stones—the level of pain felt by patients with ureteric stones seemed generally higher than that experienced by those with renal stones). Treatment in 1 patient (with a ureteric stone) was terminated earlier than intended because of severe nausea. Another patient with ischaemic heart disease being treated with beta-blockers developed a profound bradycardia and ESWL had to be stopped. He was later treated uneventfully after temporary withdrawal of beta-blockade.

There were no post-ESWL complications in 63 patients (87 treatments); 11 required injection of opiates at their home, 4 were admitted for analgesia and 2 with pyrexia were admitted and treated conservatively. Three patients with obstruction underwent ureteroscopic extraction of lower ureteric fragments. No obstructive urosepsis was seen.

Success after ESWL can be defined as complete stone clearance or can be broadened to include patients with a few residual fragments <2 mm in diameter in the absence of symptoms or infected urine. We have given results corresponding to both definitions.

**Table 1** Location of Stones

| | *No.* |
|---|---|
| *Renal stones* | |
| Upper pole | 19 |
| Middle pole | 11 |
| Lower pole | 23 |
| Multiple | 12 |
| Total | 65 |
| Pre-treatment pigtail stents (Stones >2 cm) | 6 |
| *Ureteric stones* | |
| Upper ureter | 18 |
| Mid-ureter | 5 |
| Successful retrograde manipulation | 12 |
| Treated with pigtail stent and stone *in situ* | 11 |

**Table 2** Stone Clearance Rate

| *No. of treatment sessions* | *No. of renal units treated* | *Cumulative success rate at 3 months* |
|---|---|---|
| 1 | 70 | 55 (62)* |
| 2 | 17 | 62 (74) |
| 3 | 1 | 63 (75) |
| Total | 88 | 63 (75) |

* Figure in brackets includes patients with asymptomatic residual fragments <2 mm.

Table 2 shows the stone-free rate after treatment. Four patients had no evidence of fragmentation after 1 treatment. Two of these were renal stones—1 was a cystine stone and the patient has been referred elsewhere for ESWL. The other stone was tightly impacted in an upper pole calix; an attempt at percutaneous nephrolithotomy also failed and the stone was removed by open nephrolithotomy. Two ureteric stones were removed by open ureterolithotomy after failure to fragment. Three stones failed to fragment after 2 treatments: 1 upper ureteric and 1 renal stone were removed percutaneously and the third, a renal stone, is to be re-treated. There remain 6 patients whose stones were reduced in size but not to less than 2 mm. Since they are asymptomatic they are being observed, possibly for re-treatment at a later date. They have been counted as failures of treatment.

The overall cost of hiring the lithotriptor was £36,700. Ignoring the cost of using the day-case ward and of inserting the 29 ureteric stents, the cost per patient successfully treated was £509. The cost per treatment was £343. Allowing for the revenue generated by the 21 private patients, the cost per NHS patient treated was £253.

## Discussion

It is difficult to compare the results of different series of lithotripsy because of variations in stone size and composition, length of follow-up and definition of success. However, we believe that our results (72% complete stone clearance and 85% of patients either stone-free or having only small residual asymptomatic fragments) are in accordance with the results of other series using various types of lithotriptor both with and without anaesthesia (Eisenberger *et al.*, 1985; Chaussy and Fuchs, 1986; Marburger *et al.*, 1988).

Treatment was well tolerated without anaesthesia, only 4 patients (from a total of 107 treatments) requiring pethidine. The readmission rate was low (9/107 treatments), so that day-case treatment without anaesthesia seems to be safe and acceptable to the patients.

The overall cost to the NHS was £253 per patient (excluding the cost of day care and theatre time in those patients who had pre-treatment stenting) compares favourably with the cost of percutaneous nephrolithotomy or open surgery. It would have been possible to treat more patients at each of our sessions, further reducing costs, but this would require some cross-boundary referral which has not yet occurred.

It is impossible to quantify the benefits to the patient of being treated locally, but many patients who had experienced ESWL elsewhere were very satisfied with the service. It is arguable that the complication rate is lowered by having the same urologist involved in patient selection, treatment and aftercare. It is certainly very gratifying for a urologist interested in stone disease to be able to offer this service to his patients.

We have shown day-case lithotripsy using a mobile unit to be safe and cost-effective and to provide satisfaction for both patient and urologist.

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# First UK Consensus Conference on Lithotriptor Terminology—1989

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Summary—Recommended definitions to be used in the reporting of results of lithotripsy treatment are presented. It is suggested that these are the minimum requirements for reporting such treatment.

In the autumn of 1989, representatives from each lithotriptor centre in the United Kingdom and Eire were invited to attend a consensus meeting in Edinburgh to discuss standardisation of terms used in lithotriptor treatment and reporting of the results of therapy. The aim of the conference was to agree upon definition of lithotriptor terminology and to suggest the *minimum* requirements for reporting of treatment and results. All lithotriptor centres agreed to participate; most of the participants attended in person and the remainder contributed to the debate by letter.

At the first meeting, 2 syndicate groups produced definitions which were subsequently discussed by all participants. A written summary of the conference was then sent to all participants and further comments were invited. At a second meeting in December 1989, these comments were further discussed and compiled into this report which thus sets out the consensus view of the group representing the lithotriptor centres in the United Kingdom and Eire.

## The Lithotriptor

Reports concerning lithotripsy should include details of the type of machine used in the study, the energy source and the mode of localisation.

### Type of Generator

In addition to information about the energy source, the article should contain details of the range of kV used during treatment or, if more appropriate, the power intensity setting. The manufacturer's estimate of the peak pressure produced at the focus should also be included. Where possible, this should be supplemented by detail of actual pressures delivered by the machine under study. The frequency of generation of shock waves should be stated, whether frequency of generation is constant or whether ECG or respiratory gating is used.

### Focus

A statement of the dimensions of the focus is also necessary.

### Anaesthesia

Any report should contain a clear statement of the conditions under which the treatment was administered under the following headings.

1. General anaesthesia.
2. Regional anaesthesia (spinal or epidural).
3. Cutaneous local anaesthesia (infiltration or topical).
4. Sedo-analgesia—premedication only, drug and dose and route of administration to be stated.
5. Analgesia—pre-treatment, during treatment, drug dose and route of administration.
6. None.

### Imaging

Targeting of the stone is currently performed by ultrasound or X-ray. The modality used should be indicated. With some machines, ultrasound and

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fluoroscopy may be combined and, where this is the case, reports should contain details as to which modality was used primarily.

### ESWL Monotherapy

This term is ambiguous and its use is not recommended. It is suggested that the term ESWL is used for those treatments which do not require any ancillary procedures and that where, for example, a stent is inserted as an additional procedure, this should be categorised as ESWL plus insertion of stent. Similarly, all other elective ancillary procedures such as preliminary debulking for manipulation of ureteric stones should also be stated and the proportion of patients so treated should be clearly indicated.

For those investigators who still wish to use the term monotherapy, this should be defined unequivocally in the introduction to the paper.

### Session

A session is defined as a period of lithotripsy treatment with the end point being the patient leaving the machine. Reports should indicate the number of shocks given in any one session; the mean and maximum number of shocks given should be stated. Multiple sessions may be given as a course of treatment and a statement regarding the duration over which the treatment course proceeds should be stated.

### Stone

Reports should contain details of stones, including the site, size and type. The percentage of single and multiple stones should be included. In the case of single stones, measurements should be by the size of maximum diameter with the mean and range stated. Stones should be grouped in sizes up to 1 cm, 1.0 to 1.9 cm, 2.0 to 2.9 cm and more than 3 cm in diameter and numbers in each group stated. For mulitple stones, the number and assessment of the "stone burden" should be stated. The "stone burden" is the summation of the maximum diameters.

Anatomical or pathological abnormalities, such as medullary sponge kidney and problems with drainage, should be stated. For staghorn calculi an assessment of renal function by radioisotope scanning is desirable but not essential.

It is difficult to quantify the stone burden in patients with staghorn calculi, which should be subdivided into partial and complete; a statement of the number of calices involved should be made.

### Failure of Fragmentation

The number of cases in which fragmentation has failed to occur should be stated and the time at which this is assessed should also be recorded. It is not recommended that the degree of fragmentation is reported but those investigators who wish to state a degree of fragmentation should define these terms unequivocally.

### Objectives of Treatment

It is important that the objectives of treatment are defined before the results can be assessed. For lithotripsy the main objective is to clear the treated kidney and ureter of all radiological evidence of stones. However, in some instances the objective may be simply clearance of the targeted stone or relief of symptoms. Where applied, these treatment objectives should be stated.

### Definition of End of Treatment

Present-day lithotripsy may consist of single or multiple treatment sessions carried out at intervals which may vary from daily to several weeks. A course of treatment may thus extend for some time before it is judged to be complete. The end of a treatment course is difficult to define and varies considerably in time. In most cases, the treatment will end when the stone has been adequately fragmented and the follow-up period will begin.

An additional treatment session given for residual fragments 6 months after concluding the initial course of treatment should be regarded as secondary ESWL and constitute a further treatment session. However, if desired, the number of such secondary or "stir up" sessions may be identified.

### Stone-free

Stone-free is defined as the absence of calcific opacities in the treated upper urinary tract or the absence of filling defects on the IVU or stone fragments on the ultrasound in the case of non-opaque calculi. The absence of stone fragments is normally judged by examination of a good quality plain abdominal radiograph. Plain nephrotomography may be indicated in certain cases where it is difficult to visualise the kidney or stone fragments. However, this cannot be recommended as routine assessment for all radio-opaque stones treated by lithotripsy. Similarly, intravenous urography, ultrasound and renography may also be indicated in certain cases, particularly those with non-opaque calculi, or to assess renal anatomy and function and may aid in determining if the upper urinary tract is stone-free.

### Residual Fragments

There is, as yet, no consensus view on what size of stone fragment is significant in terms of later recurrence, of stone growth, persistence of infection or of further symptoms. Long-term follow-up studies are therefore essential to investigate this. At present, residual stone fragments are defined as those for which no further treatment is planned. It is therefore recommended that residual fragments are reported according to their individual size or the overall dimensions of a collection of residual fragments. It is appreciated that measurement of small fragments is inaccurate on a plain radiograph and also that determination of the actual size of residual fragments may be impossible when they are clumped together.

If fragments of 5 mm or more remain, the lithotripsy treatment should be regarded as incomplete. Residual stone fragments should be divided into targeted or non-targeted stones and their number and size stated.

### Follow-up

The purposes of follow-up may be:

(1) To determine when no further lithotripsy treatment is required.
(2) To ascertain that all stone fragments have passed and that no early complications have occurred.
(3) Long-term follow-up may be used to assess stone recurrence rates and late complications such as hypertension.

The easiest starting point to choose for defining the follow-up period is the date of the last treatment session, excluding secondary or "stir up" sessions. The mean interval between the first and last treatment sessions and the range should be stated. The date of completion of a course of treatment has been shown to be very variable and difficult to determine. The point at which the patient becomes stone-free is also variable and may not be achieved in a considerable proportion of cases.

### Elective Intervention

Pre-lithotripsy intervention, such as percutaneous debulking and stenting, should be reported.

The only elective post-lithotripsy intervention is the removal of a stent. All others must be regarded as secondary procedures to deal with complications or treatment failure.

### Complications

Mortality and the cause of death should be stated.

The reporting of complications should be divided into major, minor and none. Major complications are defined as those requiring admission or readmission to a hospital or prolongation of a patient's hospital stay. Secondary procedures used to treat these complications, such as ureterorenoscopy, percutaneous nephrolithotomy, insertion of nephrostomy tubes or nephrectomy, should be stated. These complications should be subdivided into those requiring treatment under general aneasthesia and those not requiring general anaesthesia. The most important major complications are obstruction and infection but may include renal colic, urinary tract, gastrointestinal and pulmonary haemorrhage and pancreatitis.

Minor complications are those requiring treatment which can be managed without admission to hospital; the most common of these will be ureteric colic requiring analgesia. In most cases it will be difficult to report accurately the number of minor complications.

### Reporting results

In reporting any treatment series, it is essential that the following are clearly stated:

(1) The number of patients treated.
(2) The number of kidneys and ureters treated.
(3) The number completing the treatment course.
(4) The number assessed at a fixed time interval after completed treatment.
(5) The number proceeding to long-term follow-up.

It is agreed that the best fixed time points for assessment are 3 and 6 months after the last treatment sessions.

Thus it is necessary to state the results in terms of percentage of the *original* population of patients stone-free at x months where x is the interval after completion of treatment and time of assessment.

The percentage of patients with residual fragments of a defined size can be stated in similar terms.

For long-term follow-up the median and range of follow-up should be stated. Patients should be divided into 4 groups according to whether:

(1) They have become stone-free.
(2) They have residual fragments for which no further treatment is required.
(3) They have undergone further procedures to remove the treated stone or stone fragments.
(4) They are treatment failures for whom no further treatment is planned.

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# Management of Staghorn Stones Using a Combination of Lithotripsy, Percutaneous Nephrolithotomy and Solution R Irrigation

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Summary—The treatment of staghorn and partial staghorn calculi remains complex despite modern methods of stone removal. We describe the results following treatment of 112 stones. Three methods were used: percutaneous nephrolithotomy, extracorporeal shockwave lithotripsy and Solution R irrigation, either alone or in combination; 57 stones (55.8%) were completely cleared, with Solution R irrigation helping to achieve complete clearance in 6 of these. A further 24 stones were not completely cleared (small asymptomatic fragments <3 mm remained). A satisfactory outcome (stone-free or asymptomatic fragments <3 mm) was achieved in 81 stones (79%).

In the surgical management of partial (PS) and complete (SH) staghorn stones the kidney should, ideally, be cleared of stone to prevent recurrence. To achieve this at open operation, manoeuvres such as anatrophic nephrolithotomy (Smith and Boyce, 1968), radial nephrotomy with the use of renal hypothermia (Wickham, 1979) or Doppler probe (Rao *et al.*, 1984) have been used with modest success. The introduction of percutaneous nephrolithotomy (PCNL) and extracorporeal shockwave lithotripsy (ESWL) have dramatically changed the surgical management of urinary tract stones.

However, PS and SH stones continue to pose problems because it is not always possible to achieve complete success using one or both of these techniques. An additional approach is the dissolution of stone or stone fragments with solutions containing citric acid and magnesium ions.

We describe our experience in the management of these difficult stones using these 3 methods of treatment either alone or in combination.

## Patients and Methods

The results of treating 110 patients (72 females and 38 males aged between 3 and 84 years; mean 52 years) with 112 stones have been reviewed.

There were 67 partial staghorn stones involving the renal pelvis and 1 or 2 poles of the kidney and 45 complete staghorn stones involving the renal pelvis and all 3 poles of the kidney. Subsequent X-ray diffraction analysis showed that 97 stones (86.6%) were composed of struvite, 14 (12.5%) were calcium oxalate monohydrate and/or calcium oxalate dihydrate and 1 stone (0.8%) was pure brushite.

At the time of initial treatment 64 patients (58%) had active urinary infection (bacterial growth on mid-stream specimen of urine). All patients were given appropriate broad spectrum parenteral antibiotic cover during treatment.

Three methods were used: percutaneous nephrolithotomy, extracorporeal shockwave lithotripsy and Solution R irrigation (Uro-Tainer, ClinMed Ltd, High Wycombe).

The larger stones (>3 cm long and 1 cm wide on X-ray) were usually subjected to percutaneous debulking and a double-J stent was passed antegradely if significant stone remained at the end of the procedure. ESWL was then used to fragment any remaining stone. When percutaneous debulking failed or the procedure was unacceptable to the patient, the stones were subjected to primary ESWL

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after placing a double-J ureteric stent. Some SH stones of low radiological density and without extensive caliceal extensions and PS stones <3 cm long and 1 cm wide were similarly subjected to primary ESWL after the placement of a double-J stent. Open surgery was used only if PCNL and ESWL failed.

ESWL was performed under local skin infiltration anaesthesia using a Siemens "Lithostar" lithotriptor. When a double-J stent was indicated it was inserted under general or regional anaesthesia at the time of the first ESWL session. A forced "diuresis" was used during all ESWL sessions; this was achieved by administering 2 l of Hartman's solution and 40 mg frusemide intravenously, or by irrigating the kidney with normal saline through a nephrostomy tube if one was in place. A small urethral catheter was used to drain the bladder.

The kidney was irrigated with solution R (Table 1) under the following circumstances: (1) PCNL had failed but a nephrostomy tube could be left *in situ* and the stone was deemed unsuitable for primary ESWL because of stone burden and radiological density. (2) After percutaneous debulking when there was still a large stone burden, particularly when 1 or more peripheral stones were over 2 cm in diameter and of high radiological density. (3) Fragments had failed to clear after successful fragmentation by ESWL, particularly if present in dilated calices and a nephrostomy tube was *in situ*.

The kidney was irrigated with Solution R through a 7F pigtail nephrostomy tube at the rate of 50 ml/h. To ensure drainage of the solution to the bladder a double-J ureteric stent was inserted if one was not already in place. Before commencing the irrigation an antegrade nephrostogram was performed to check that drainage from the kidney was adequate and also to exclude extravasation; the kidney was then perfused with normal saline for 12 h, followed by irrigation with Solution R. During irrigation the urine of all patients was monitored for infection and broad spectrum antibiotics were used. Blood urea and electrolyte levels were measured on alternate days and the serum magnesium on every third day. The irrigation bag was kept as low as possible to prevent excessive pressure within the collecting system.

**Table 1** Composition of Solution R

| | |
|---|---|
| Citric acid | 6% |
| Gluconolactone | 0.6% |
| Light magnesium carbonate | 2.8% |
| Di-sodium edetate | 0.01% |

The success of all forms of treatment was judged by plain abdominal X-ray. If any doubt existed, further films were taken after a thorough bowel clearance and tomographic cuts were made if further clarification was needed.

## Results

A total of 47 PCNL debulkings, 319 ESWL sessions and 13 courses of Solution R irrigation were used in 110 patients with 112 stones; 3 open operations were performed after failed access for PCNL.

Ten patients were lost to follow-up and results were therefore available on 100 patients with 102 treated renal units. It was found that 57 renal units (55.8%) were radiologically clear of stone with a mean follow-up of 8.2 months. Two kidneys were cleared by PCNL alone and 29 by ESWL alone; 17 were cleared by a combination of PCNL and ESWL and 4 by PCNL plus ESWL and solution R irrigation. Two renal units needed ESWL plus irrigation to achieve clearance. The 3 patients who had open surgery required ESWL after this to eradicate small residual fragments. One of the patients who underwent irrigation had a pure brushite stone; in this case PCNL failed because neither the electrohydraulic nor the ultrasound probe would fragment the stone adequately. Solution R dissolved over 75% of the stone and ESWL was effective against the remainder.

In all, 45 renal units (44.2%) were not completely cleared of stone. Of these, 24 patients are asymptomatic with residual fragments <3 mm; 21 have fragments >3 mm. Table 2 shows the treatments used and the results in all 102 renal units. It is expected that further treatment will be given to some of the patients with residual stone and an improved overall clearance rate achieved.

Three patients had steinstrasse after ESWL despite the presence of a double-J stent in each case. They were all treated by ESWL to the impacted leading stone fragment with subsequent spontaneous passage of all stone debris. Haematuria was universal but transient in patients after ESWL. During Solution R irrigation 2 patients developed severe hypokalaemia and 1 developed hypermagnesaemia. One of the patients with hypokalaemia developed muscle weakness. Despite this, however, he and the others all improved clinically and biochemically on stopping the irrigation, which was then restarted after an interval of at least a week.

**Table 2** Results of Treating 102 Staghorn Stones

| *Treatment* | *Clear* | *Fragments <3 mm* | *Fragments >3 mm* |
|---|---|---|---|
| PCNL alone | 2 | — | — |
| PCNL+ESWL | 17 | 8 | 4 |
| PCNL+ESWL+irrigation | 4 | 1 | 3 |
| ESWL alone | 29 | 14 | 14 |
| ESWL+irrigation | 2 | 1 | — |
| Open+ESWL | 3 | — | — |
| | n=81 (79%) | | n=21 (21%) |

PCNL: Percutaneous nephrolithotomy. ESWL: Extracorporeal shockwave lithotripsy. Irrigation: Irrigation with Solution R. Open: Open stone surgery.

Twenty patients developed pyrexia after PCNL and blood cultures were positive in 5 of these. All settled with continued antibiotic therapy.

## Discussion

Surgical removal of partial and complete staghorn stones is a challenging task. During conventional open surgery, procedures such as anatrophic nephrolithotomy (Smith and Boyce, 1968), renal hypothermia (Wickham, 1979) and the use of Doppler ultrasound (Rao *et al.*, 1984) have helped clearance by improving access to peripheral caliceal stones. Despite these manoeuvres and the exposure of the patient to the risks of major surgery, complete clearance is possible in only 65 to 76% of cases (Wickham *et al.*, 1974; Giuliani *et al.*, 1988).

The advent of endoscopic percutaneous surgery has offered a less invasive method of removing renal stones but has several disadvantages when dealing with SH and PS stones. It is not always possible to gain access to the kidney and even if this is achieved, complete stone clearance is not always possible. Multiple tracts may aid satisfactory clearance by allowing access to peripheral stone but this involves multiple anaesthetics and prolonged periods of hospitalisation (Winfield *et al.*, 1988). There may also be a greater risk of complications. The use of a flexible nephroscope can aid access to a peripherally placed stone but it may not be possible to disintegrate or extract the stone by this means. An additional problem is that some stones are resistant to the usual methods of lithotripsy employed during PCNL or ureteroscopy (Dretler *et al.*, 1987).

The advent of ESWL (Chaussy *et al.*, 1980) initially promised a completely non-invasive method of stone eradication. However, it became apparent that primary ESWL for large PS and SH stones was not the complete answer, since stone clearance is inversely proportional to the stone burden (Gleeson *et al.*, 1989; Sandhu and Rao, 1989). ESWL has been shown to clear only about 50% of stones exceeding 3 cm in size (Gleeson and Griffith, 1989). Furthermore, some stones fail to fragment into small pieces and others may need several ESWL sessions to achieve adequate fragmentation (Riehle *et al.*, 1986). Even with good fragmentation, the resulting large bulk of stone debris may cause ureteric obstruction despite the use of a double-J ureteric stent (Riehle *et al.*, 1986).

Thus a combination of PCNL and ESWL may be necessary in the treatment of some PS and SH stones (Dickinson *et al.*, 1986; Schulze *et al.*, 1986; Das *et al.*, 1987), but problems arise if the residual stone burden after PCNL is still large and if fragments in the kidney fail to clear after ESWL.

Two major questions therefore remain unanswered. How long should one wait before giving further ESWL? Is is better to wait and re-treat when the stone has re-grown or should further treatment be carried out early? In addition, if the residual stone is large and dense, should multiple PCNL sessions be used? These questions led us to examine another adjuvant method of treatment—stone dissolution. An isotonic solution of citric acid containing magnesium ions was first described over 40 years ago and has been used after open surgery to eradicate remaining stone fragments (Suby and Albright, 1943). Although the use of irrigation to dissolve stones seems attractive, it is a slow process and prolonged irrigation can lead to 2 potentially severe biochemical problems. Hypokalaemia and hypermagnesaemia may occur independently or simultaneously, as happened in the present series. These problems can be minimised if a nephrostogram is performed prior to irrigation to exclude extravasation. In addition, the irrigation pressure should be kept low to avoid excessive pressure within the renal pelvis. The serum electrolyte and magnesium levels should be measured frequently and the possibility of a biochemical problem considered if any patient undergoing irrigation with such a solution becomes ill for no apparent reason.

The other possible severe complication of dissolution therapy is the introduction of bacterial contamination. Although this could be a problem when hemiacidrin solution is used, owing to difficulties in preparation of the solution, the use of pre-packed sterile containers of Solution R has, in our experience, resulted in no infective complications. Prophylactic antibiotics used during irrigation may also have contributed to this low incidence.

We now consider dissolution therapy to be the third method of stone removal. Any renal stone which shows reluctance to fragment with either PCNL or ESWL can be "softened" with irrigation prior to further attempts at treatment with ESWL. In some cases complete eradication may occur with irrigation alone. Stone fragments which refuse to clear after ESWL (or PCNL) can be dissolved with irrigation therapy and we have cleared 6 renal units of stone by this adjuvant method.

The results of treating patients with staghorn stones vary greatly, depending on factors such as stone burden and configuration, the presence or absence of dilatation of the collecting system, stone composition and treatment used. Stone-free rates range from 23% (Segura *et al.*, 1987) to 73% (Fuchs and Chaussy, 1987), demonstrating the importance of planning treatment on an individual basis. The recurrence of stones following treatment varies. After complete removal by open surgery Boyce and Elkins (1974) reported a rate of 17%, whereas Patterson *et al.* (1987) reported a 9% recurrence rate following complete removal by percutaneous surgery. A similar rate of 9% was reported by Newman and Scott (1987) after using ESWL to render patients stone-free. In contrast, the rate of stone re-growth in patients not rendered stone-free is higher. A rate of 22% was noted by Newman and Scott (1987) and Patterson *et al.* (1987) recorded 62.5%. This is often due to persistence of infection in the presence of intact residual stones. It has been demonstrated that such continuance of urinary infection is less likely to occur when modern techniques are used, even if residual fragments remain (Pode *et al.*, 1988; Rassweiler *et al.*, 1990), possibly because antibiotics have a better chance of "sterilising" the fragmented stone than an intact one.

We have completely cleared 57 renal units (55.8%). A further 24 renal units still retain a few small fragments but we feel they are too small to re-treat and with longer follow-up they may clear spontaneously. Thus in 81 cases (79%) the outcome was satisfactory. Some of the remaining 21 patients with residual stone fragments >3 mm will receive further treatment and we anticipate a further increase in the stone-free rate. However, longer follow-up is necessary to determine stone re-growth/recurrence rates in these patients.

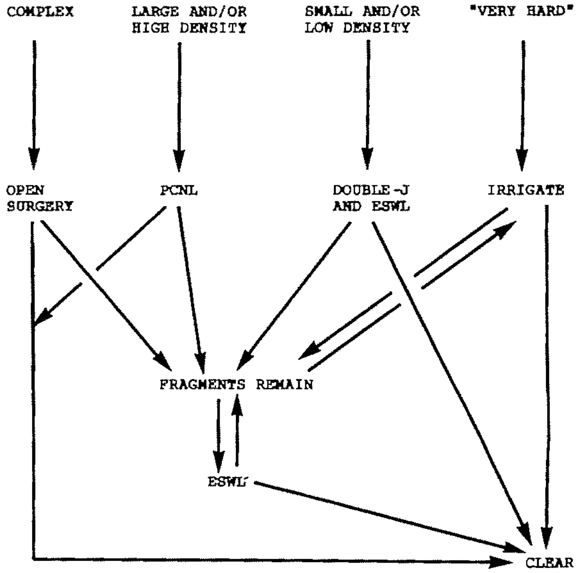

**Fig.** Treatment plan for staghorn stones. Complex: large multi-branched stone filling collecting system completely. High density: stone with very dense homogenous appearance on plain X-ray. Low density: stone with thin heterogeneous appearance on plain X-ray. "Very hard": stone which fails to fragment with either ESWL or PCNL.

The treatment of SH and PS stones is difficult even with the modern methods available today. The overall stone-free rate is lower than after open surgery, but the patients with residual fragments are asymptomatic and have a lower risk of infection and recurrence. To achieve the best results a combination of all treatment modalities may have to be used, the treatment being tailored for each individual patient. This may be achieved by following the treatment plan outlined in the Figure.

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# The Impact of Extracorporeal Piezoelectric Lithotripsy on the Management of Ureteric Calculi: an Audit

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Summary—The presentation and management of 153 patients with ureteric calculi requiring active treatment over a 12-month period were reviewed; 74% of patients had primary ureteric calculi and 26% had ureteric calculi composed of fragments resulting from extracorporeal piezoelectric shockwave lithotripsy (EPL) to renal calculi; 32 patients (21%) had more than 1 calculus or a steinstrasse.

The primary procedures included were *in situ* EPL ($n=54$), push-bang (44), retrograde ureteroscopy (40), Dormia basket extraction (6), push-pull (1), antegrade ureteroscopy (1) and combinations of these (7). The success of the primary procedure could not be predicted from stone size, site or duration in the ureter, but upper tract dilatation was significantly less ($p<0.01$) in the successful group. The overall success rate for complete stone extraction was 97%, but 54 patients (35%) required more than 1 procedure to achieve this. *In situ* EPL and push-bang, as either primary or secondary procedures, were successful in treating 79 patients (52%); 2 patients required ureterolithotomy (1.3%). The overall complication rate was 18%.

Since EPL is only successful in treating approximately half of ureteric calculi, a range of other treatments should be available to maintain a low rate of open surgery.

During the past decade there has been a rapid development in equipment for the endourological extraction of ureteric calculi. Percutaneous techniques have been refined, allowing both antegrade and conventional retrograde access to the ureter. More recently, extracorporeal shockwave lithotripsy (ESWL) has become available in many centres for the treatment of renal calculi. ESWL can also be used to treat some ureteric calculi either *in situ* or after preliminary manipulation into the renal pelvis (push-bang). This treatment may produce obstructing fragments in the ureter, which are sometimes multiple and may occur at more than 1 site. Thus the presenting features and treatment options for ureteric calculi have become increasingly complex.

The aims of this review were 3-fold. First, to examine the impact of extracorporal piezoelectric shockwave lithotripsy on our practice. Second, to attempt to identify the optimal method of treatment of ureteric stones. Finally, to provide a detailed audit against which the results of introducing innovations such as laser lithotripsy and fine electrohydraulic probes can be compared.

## Patients and Methods

The presenting features, treatment and outcome of 153 patients presenting with ureteric calculi which required surgical treatment over a 12-month period commencing in February 1988 were reviewed retrospectively. Data were entered and analysed on a spreadsheet/database program (Microsoft Excel) using a Tandon PCA 40 IBM compatible personal computer.

There were 108 male and 45 female patients. Their mean age was 51 years (range 13–86); 89 patients (58%) were referred from outside Lothian Health Board.

The site and characteristics of the stones are shown in Table 1. The mean stone size was 15 mm (range 4–54). In 40 cases the ureteric calculi were

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**Table 1** Characteristics of Calculi and Sites

| | *Single stone* | *Multiple* | *Steinstrasse* |
|---|---|---|---|
| Upper ureter* | 42 | 0 | 3 |
| Mid-ureter* | 42 | 1 | 7 |
| Lower ureter | 36 | 0 | 16 |
| Multiple sites | 0 | 5 | 0 |
| Transplant ureter | 1 | 0 | 1 |

*The upper ureter was classified as extending to the lower pole of the kidney, with the mid-ureter extending beyond to the pelvic brim.

fragments resulting from treatment of renal calculi by EPL. The length of time that the stone had been in the ureter before commencing treatment was unclear in 4 cases. The mean duration for the remainder was 91 days (range 1–558). Renal drainage, for relief of acute obstruction had been performed prior to referral in 22 patients (double pigtail stent 14, percutaneous nephrostomy 8). Three patients had undergone unsuccessful attempts at Dormia basket extraction before referral. An intravenous urogram (IVU) and/or ultrasound scan demonstrated gross obstruction in 6 patients, varying degrees of upper tract dilatation in 88 and no evidence of obstruction in 20. No information was available on 31 patients.

The primary procedures were *in situ* EPL, push-bang, antegrade ureteroscopy, push-pull, retrograde ureteroscopy and Dormia basket extraction. In some cases a combination of these procedures was required. In others, where one method of extraction failed, another was substituted under the same general anaesthetic.

### *In situ EPL*

This was carried out on a Wolf 2300 Piezolith. The machine generates shockwaves by means of a piezoelectric mechanism and neither analgesia nor anaesthesia is required (Marberger *et al.*, 1989; Neerhut *et al.*, 1989). Ultrasound is used to localise stones and *in situ* treatment is, therefore, mainly feasible for upper ureteric calculi, although some mid-ureteric calculi or steinstrassen near the vesicoureteric junction can sometimes be imaged.

### *Push-bang*

Stones in the upper and mid-ureter were manipulated back into the kidney using an 8 F angiocath passed over a guidewire or a conventional ureteric catheter passed via a cystoscope. A combination of flushing with a 1:2 mixture of 2% lignocaine gel and isotonic saline and direct pushing was carried out, while movement of the stone was monitored with an image intensifier C-arm. The patient was transferred for EPL immediately after reversal of anaesthesia. The ureteric catheter was not removed until a post-treatment radiograph had demonstrated adequate fragmentation of the calculus.

### *Antegrade ureteroscopy*

This was carried out with the patient lying in the prone position under general anaesthesia. A percutaneous tract was created through a mid or upper pole calix under image intensifier control. A Storz nephroscope or Storz 13 F ureteroscope was inserted through an Amplatz sheath into the upper ureter. The stone was either grasped with forceps and removed intact or was fragmented by direct contact with an ultrasound probe and fragments removed with forceps. A 10 F Cope loop nephrostomy drain was inserted for 24 to 48 h postoperatively. Antegrade ureteroscopy was used as the primary procedure only in patients who had required a percutaneous nephrostomy for obstruction and/or infection. It was carried out more frequently as a secondary procedure following failure of retrograde manipulation.

### *Push-pull*

The ureteric calculus was manipulated back into the kidney by the technique which has already been described. A percutaneous tract was dilated and the stone removed with a Storz nephroscope either with or without preliminary fragmentation by direct contact with an ultrasound probe. It was used only once in this series, for removal of a calculus from the ureter of a transplanted kidney.

### *Retrograde ureteroscopy*

This was carried out as previously described (Tolley, 1989), using either 13 F Storz, 11.5 F Wolf or 9.5 F Wolf short ureteroscopes. The ureteroscope was advanced to the level of the stone, usually following preliminary dilatatation of the ureteric orifice and intramural ureter with a 4 F Fogarty balloon catheter under direct vision. Smaller stones (<9 mm) were engaged in a 4 F Pfister-Schwarz stone basket under vision and then the ureteroscope and basket were gently withdrawn. Larger calculi were fragmented by means of direct contact with the ultrasound probe and fragments removed with grasping forceps. The ureter was then reinspected to check that there was no perforation. A 4 F ureteric catheter was inserted under vision, secured to a 16 F latex Foley bladder catheter and left *in* *situ* for 48 h. When it was impossible to reach the level of the stone at the primary procedure, a 4.8 F double pigtail ureteric stent (Lewis Medical) was inserted to allow ureteric dilatation to occur (Ramsay *et al.*, 1985). The ureteroscopy was then repeated 2 to 3 weeks later. Retrograde ureteroscopy was used for lower ureteric and some mid-ureteric stones.

*Dormia basket extraction*

This was limited to calculi (<10 mm) near the ureteric orifice. The basket was introduced and the stone engaged while monitoring with image intensifier control. No drainage catheter was inserted.

All patients were given a prophylactic dose of intravenous cephalosporin administered at the time of induction of anaesthesia, prior to the endourological procedure.

Statistical comparisons were made by the $\chi^2$ test.

## Results

Details of the primary procedures are given in Table 2. They were judged as successful when the stone bulk was completely removed, partially successful when only part of the stone was removed, and failures when none of the stone was removed. Using these criteria, 93 primary procedures were successful (61%), 11 were partially successful (7%) and 49 were failures (32%). Stone duration, size, site and the presence of a dilated upper tract are compared for successful cases and partially successful cases plus failures in Table 3. The proportion of patients with upper tract dilatation was less in the successful group ($P<0.01$). None of the other parameters significantly affected the outcome.

Six patients with failed or incompletely successful primary procedures required a percutaneous nephrostomy to be inserted under local anaesthesia within 48 h.

Of the 14 patients who had a stent inserted prior to referral, 9 were treated with *in situ* EPL as the primary procedure. This was successful in only 1 patient. Six required removal of the stent plus a push-bang; 1 required further *in situ* EPL after stent removal and 1 underwent a Dormia basket extraction.

Details of further procedures which were carried out on patients who did not have a completely successful primary procedure are shown in Table 4. Four patients passed the stone or fragments spontaneously before discharge from hospital and a further 2 patients had 2-mm ureteric fragments which were expected to pass spontaneously. Fifty-four patients (35%) required more than 1 procedure to render them stone-free and 2 patients (1.4%) required a ureterolithotomy.

A total of 79 patients (52%) were treated successfully with either *in situ* EPL or a push-bang as primary and secondary procedures. Of 49 successful push-bangs, carried out as either primary or secondary procedures, 21 required more than 1 session of EPL to fragment the stone completely.

Complications developed in 27 patients (18%). The largest group consisted of 10 patients who developed further obstructing ureteric fragments after lithotripsy or antegrade ureteroscopy. Their

**Table 2** Primary Procedures and Success Rates

| *Primary procedures* | | *% Successful* |
|---|---|---|
| *In situ* EPL | 54 | 44 |
| PB | 44 | 77 |
| PB+AU | 1 | |
| PB+RU | 3 | |
| PB+PERC | 1 | |
| PP | 1 | |
| AU | 1 | |
| RU | 40 | 65 |
| RU+DB | 1 | |
| RU+PP | 1 | |
| DB | 6 | 83 |

EPL: Extracorporeal piezoelectric lithotripsy. PB: Push-bang. AU: Antegrade ureteroscopy. PERC: Percutaneous nephrolithotomy. PP: Push-pull. RU: retrograde ureteroscopy. DB: Dormia basket. In 7 cases a combination of these procedures was carried out.

**Table 3** Comparison between Completely Successful Cases and Partially Successful Cases plus Failures

| | *Successful (n=93)* | | *Partially successful+failures (n=60)* |
|---|---|---|---|
| Mean size (mm) | 14 | | 16 |
| Mean duration (days) | 91 | | 93 |
| Site—upper | 26 | | 19 |
| mid | 31 | | 19 |
| lower | 30 | | 22 |
| multiple | 5 | | 0 |
| transplant | 1 | | 0 |
| Dilated upper tract or obstructed | 53 | $P<0.01$ | 44 |

The proportion of patients with a dilated or obstructed upper tract was significantly less ($P<0.01$) in the successful group. There were no significant differences between the groups for stone size, duration in the ureter and site.

treatment is included in the list of further procedures (Table 4).

Retrograde ureteroscopy resulted in 5 ureteric perforations. In 2 of these cases a double pigtail stent was inserted for 6 to 8 weeks and in another a temporary ureteric catheter was inserted. The remaining 2 patients needed a temporary percutaneous nephrostomy. All have been followed up with no evidence of stricture formation at a mean of 102 days (range 46–159).

Four patients developed ureteric strictures, 3 following retrograde and 1 following antegrade ureteroscopy. Two were treated with dilatation and double pigtail stenting, but the other 2 patients required open reimplantation. Three of the 4 had undergone ureteric dilatation with a Fogarty balloon catheter. This compared with 75% of all patients who underwent retrograde ureteroscopy. Ultrasound disintegration was required in 43% of all ureteroscopies. Two strictures and 1 perforation occurred in this group.

Double pigtail stents, inserted in 2 patients with additional large renal calculi, migrated and needed to be replaced; 2 patients developed septicaemia, 1 associated with acute renal failure. Both made a complete recovery after transfer to an intensive care unit. One patient received labial burns from overheating of an ultrasound probe. One patient developed clot retention after a Dormia basket extraction. In another case pus was noted to drain from the kidney at the time of a push-bang. This patient received EPL but was later found to have a non-functioning kidney and underwent nephrectomy. It is likely that the kidney was already non-functioning at the time of the primary procedure, but we have included this as a possible complication.

**Table 4** Further Procedures or Outcome for Patients with Partially Successful or Failed Primary Procedures

| Procedure<br>*First* | *Second* | *Third* | *Fourth* |
|---|---|---|---|
| 30 *in situ* EPL | 10 PB | 3 AU | 1 RU |
| | 6 Stent removal+PB | 1 DB | |
| | 8 RU | | |
| | 2 DB | | |
| | 1 Stent removal+DB | | |
| | 1 Stent removal+*in situ* EPL | | |
| | 1 AU | | |
| | 1 RU+PERC | | |
| 10 PB | 3 AU | | |
| | 3 RU | | |
| | 2 *In situ* EPL | | |
| | 1 PB | | |
| | 1 RU+PERC | | |
| 1 PB+AU | 1 RU | | |
| 1 PB+PERC | 1 Ureterolithotomy | | |
| 1 PB+RU | 1 RU | | |
| 1 AU | 1 RU | | |
| 14 RU | 7 RU | 1 Ureterolithotomy | |
| | 3 Passed spontaneously | | |
| | 2 Fragment <3 mm | | |
| | 1 *In situ* EPL | | |
| | 1 AU | | |
| 1 RU+DB | 1 PB | | |
| 1 DB | 1 Passed spontaneously | | |

Abbreviations as in Table 2.

One patient was lost to follow-up after receiving *in situ* EPL to a lower ureteric calculus. The mean length of follow-up for the remainder was 99 days (range 1–496) and 149 patients (97%) are now stone-free. Two patients have small residual fragments (<3 mm).

## Discussion

There has been much debate recently about the importance of surgical audit. In fields where new techniques and expensive capital equipment are being introduced, audit is likely to be of particular value. More powerful microcomputers and refined software increase the amount of data which can be processed and simplify their analysis. Although this study has the inherent deficiencies of any retrospective review, it has allowed us to refine our data collection system and details of all endourology carried out in this centre are now collected prospectively.

We were particularly interested in the impact of EPL on the presentation and management of ureteric calculi. Over a 4-year period commencing in 1983, prior to the introduction of EPL, 184 patients required surgery for ureteric stones (Tolley, 1989). Since the indications for surgical intervention remain unchanged, the introduction of a lithotriptor serving Scotland has led to an approximately 3-fold increase in the number of ureteric calculi which are treated here. This is partly due to obstructing ureteric fragments resulting from EPL (40 of 629 patients treated during the period of the study) but also because the Scottish Lithotriptor Centre has been funded to provide a referral service for stone patients since 1988. EPL either *in situ* or after retrograde manipulation was successful in approximately half of the ureteric stones. EPL has also altered the character of stones which are now being treated. Steinstrassen and multiple stones

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comprised 21% of this series and the management of these patients is inherently more complex and difficult.

It was surprising to find that the success of the primary procedure could not be predicted from size, duration and site of the stone. Others have also found that upper tract dilatation is associated with a significantly lower rate of success (Sanseverino *et al.*, 1988) and this is possible related to a greater degree of impaction.

Our success rate for primary procedures appears very low. This is because we have preferred to carry out a trial of EPL *in situ*, since this is non-invasive and anaesthesia-free. When deciding on the management of a patient with a ureteric calculus it is appropriate to balance the invasiveness of each treatment option with the likelihood of success. *In situ* EPL is obviously the least invasive technique, but imaging by ultrasound limits its effectiveness mainly to the upper ureter. In our hands it was successful in 51% of patients who did not have a double pigtail stent in the ureter. In patients with a calculus lying alongside a double pigtail stent the success rate dropped to only 11%, and in this situation it seems unreasonable to attempt treatment with *in situ* EPL Furthermore, it is well recognised that ureteric calculi require more shocks to achieve fragmentation than do calculi within the kidney (Lingeman *et al.*, 1987). Our experience with the Wolf 2300 machine suggests that large stones (>15 mm) in the upper ureter frequently require several treatment sessions and under these circumstances it may be preferable to proceed directly to a push-bang. With *in situ* treatment of large stones there is also a risk of partial fragmentation, with the fragments causing further obstruction lower in the ureter.

Experience prior to the introduction of EPL suggested that mid-ureteric calculi were the most problematical to treat by endourological means (Tolley, 1989). In the present series the success rate for these stones was similar to that for stones in the upper and lower ureter. Many of the mid-ureteric stones were treated by push-bang and it seems that this technique is the initial treatment of choice for most calculi in this site. In our hands the success rate for retrograde dislodgement as a primary procedure was 77%, whereas others have reported a slightly higher figure (Lingeman *et al.*, 1987). Because of this, we now prepare patients for antegrade ureteroscopy under the same anaesthetic, should retrograde dislodgement fail. Antegrade ureteroscopy and push-pull remain valuable options for patients who develop obstructing ureteric fragments following EPL and who still have considerable stone bulk in their kidney. Under these circumstances we prefer to remove both the ureteric and renal stones through a single percutaneous tract rather than risk further episodes of ureteric obstruction with EPL. Retrograde ureteroscopy continues to have a fundamental role in the extraction of primary lower ureteric stones and in the removal of steinstrassen produced by EPL.

Initial experience with a first generation lithotriptor using X-ray localisation suggested that *in situ* ESWL was successful in only 60% of all ureteric stones (Miller *et al.*, 1985). This may be because a layer of water surrounding the stone is necessary for the cavitation effect and for dispersal of fragments. More recently, Holden and Rao (1989) treated 207 patients with a second generation machine also using X-ray localisation. At the time of the report, complete follow-up details were available for 133 patients and 89% were stone-free. If these results are confirmed it will be an important consideration when choosing and designing equipment. At present in the United Kingdom many second generation lithotriptors, such as ours, have facilities for ultrasound localisation only.

The overall complication rate of 18% is very similar to the 17.5% reported from a large series of open ureterolithotomy carried out at the Mayo Clinic (Furlow and Bucchiere, 1976). However, modern stone surgery is associated with a shorter hospital stay and the ability to recommence employment returns much more quickly.

Further obstructing ureteric fragments occurred after several different procedures. This complication could possibly have been diminished by inserting double pigtail stents more frequently. Some groups routinely insert stents following successful retrograde dislodgement (Lingeman *et al.*, 1986). We prefer to insert a temporary ureteric catheter which can be removed without a further cystoscopy and which is less expensive (£2/ureteric catheter; £58/stent). Almost half of the patients required more than 1 session of EPL after a successful push. Recently, we have delivered more shocks/session to these stones in order to reduce the number of treatment sessions and to pulverise the stones more completely. This might reduce the development of further obstructing fragments in the ureter.

Ureteric perforation occurred in patients during retrograde ureteroscopy, but this did not result in stricture formation. However, it was disappointing that 4 other patients did develop strictures. It is suggested that failure to dilate the ureter may influence stricture formation, but 3 of these patients did undergo balloon dilatation and this was similar to the rate of dilatation for all retrograde ureteroscopies. Furthermore, the use of the ultrasound probe did not influence the development of strictures or perforations. A double pigtail stent could have been inserted more frequently and ureteroscopy postponed while waiting for dilatation of the ureter. This might have reduced the stricture rate. However, the use of smaller ureteroscopes is probably the ideal solution, since the insertion of a double pigtail stent increases the number of general anaesthetics which patients receive and the presence of a double pigtail stent may cause significantly symptoms (Pollard and MacFarlane, 1988).

In summary, the introduction of EPL has had a significant effect on ureteric stone surgery in this unit. A large proportion of patients can now be treated by non-invasive or minimally invasive techniques, and ureterolithotomy has become rare. Audit has allowed us to refine management strategies. Approximately one-third of patients will require a further procedure and it is important to explain this before commencing treatment. Since it is impossible to predict the outcome, treatment options must be kept open. These options should be viewed as being complementary to each other rather than being mutually exclusive. Adopting this approach allows for the most complicated of ureteric stones to be dealt with successfully. These results must now be compared with those after introduction of innovations such as laser lithotripsy using smaller calibre instruments.

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# Do Extracorporeal Shock Waves Affect Urinary Excretion of Glycosaminoglycans?

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Summary—Urinary excretion of glycosaminoglycans (GAGs) was studied in 9 anaesthetised dogs and 10 patients with single kidneys. The animals were studied for 4 to 5 hours after administration of shock waves to 1 kidney, the contralateral organ serving as control. Urinary excretion of GAGs was measured on both sides. The patients were studied 0 to 24 and 32 to 56 h after extracorporeal shock wave lithotripsy (ESWL). In the animals an increased mean urinary excretion of GAGs was observed on both sides; this was more marked in the treated kidney. The increase reflects tissue injury in the exposed kidney induced by the extracorporeal shock waves. No increase in mean urinary excretion of GAGs was observed in the patients.

The endothelium lining the urinary tract has a surface glycosaminoglycan/mucus coat which has anti-adherence properties against bacteria, proteins and urinary crystals (Parsons *et al.*, 1977, 1980, 1985; Gill *et al.*, 1982; Grenabo *et al.*, 1988). The protective effect probably depends on the hydrophilic nature of the sulphated GAGs.

In the tissue they are present as proteoglycans, *i.e.* polypeptide cores with acidic glycosaminoglycan side chains. Being proteoglycans, GAGs are widely distributed in basement membranes and are present in all renal tissue basement membranes and cell membranes (Stow *et al.*, 1985). In the glomerular basement membrane they represent important structural components required for the maintenance of its selective permeability properties (Farquhar, 1981). They are excreted in normal human urine as degraded chondroitin sulphate and heparan sulphate (MW ≈ 13000) (Scott and Newton, 1975).

Knowledge of the renal handling of GAGs after exposure to shock waves is of clinical interest, since GAGs play an important part in local defence against infection and may prevent stone particles from adhering to the urothelium.

This study was performed to investigate whether extracorporeal shock waves alter the urinary excretion of GAGs and is, to our knowledge, the first report on the subject.

## Material and Methods

### *Animals*

Nine female English Setter dogs weighing 16 to 21 kg were used. They were deprived of food for 12 h before the experiment but had free access to water. General anaesthesia was induced with pentobarbital 25 mg/kg body weight and maintained by repeated small doses as required. Spontaneous respiration was maintained through an endotracheal tube. Infusions were administered via a peripheral paw vein. Arterial blood pressure was monitored at regular intervals via a percutaneously placed transfemoral aortic catheter.

A low midline mini-laparotomy was performed and a 7F ureteric balloon catheter inserted into the lower ureter on each side for selective urine collection. Bilateral selective renal vein catheters were placed via a percutaneous transfemoral approach.

Ringer acetate was infused at a rate of 5 ml/min throughout the experiment. As part of renal

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physiological studies (Karlsen *et al.*, 1990), a priming dose and sustaining infusion of 5% inulin (Inulin, Laevosan International AG, Zürich, Switzerland) were adjusted to keep plasma inulin concentration within 20 to 30 mg/100 ml. When urine flow was stable, urine sampling from each kidney was started. Three collecting periods of at least 30 min (control periods, marked 1, 2, 3, in the Figure) were completed before the administration of shock waves, and 4 periods of at least 30 min following treatment (treatment periods, marked 4, 5, 6, 7 in the Figure). The first urine sample after the administration of shock waves was collected immediately after exposure. Mean urine flow in the control periods was 2.0 ml/min in the kidney to be treated and 1.6 ml/min on the contralateral side. Blood was sampled from the aorta and each renal vein at the time of urine collection for additional physiological analyses.

The original Dornier HM-3 lithotriptor was used in 3 dogs and the updated, modified version (Graff *et al.*, 1987) in 6. The animals were secured in the supine position by strapping padded paws to the surrounding structures of the gantry. Submersed in the degassed water bath (maintained at 37°C), the dogs were subjected to shock waves aimed at 1 kidney, the contralateral, non-exposed kidney serving as control.

The waves were focused by 2-plane fluoroscopy on the renal pelvis, visualised by a thin, very flexible guidewire momentarily inserted via the ureteric occlusion catheter, to curl up in the pelvis. The relations of the guidewire (renal pelvis) to the tip of the renal vein catheter and surrounding bony landmarks were carefully noted and the guidewire immediately removed.

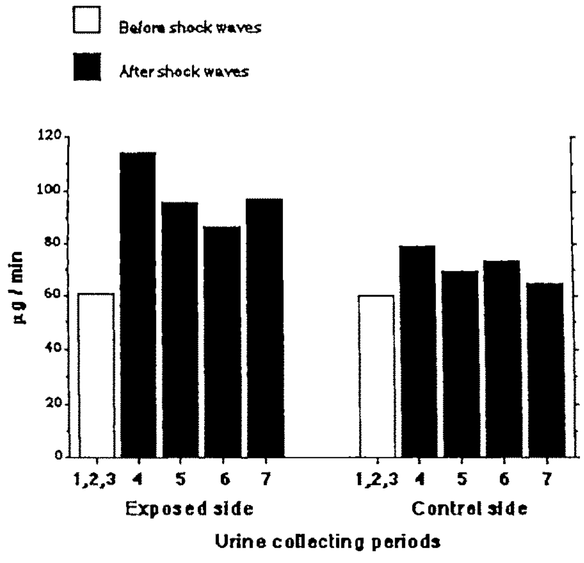

**Fig.** Mean urinary excretion of GAGs in dogs (µg/min) before (1, 2, 3) and during the 4 collecting periods after (4, 5, 6, 7) the administration of shock waves to 1 kidney.

The dogs treated by the Dornier HM-3 lithotriptor received 1500 impulses at 18 to 20 kV; those subjected to the modified generator received 2000 impulses at an equivalent voltage range. The impulses were manually triggered at a rate of 70/min. The mean time of water immersion was 19 min (range 15–30).

*Patients*

For accurate assessment of the changes occurring in the treated kidney, patients with 1 functioning kidney only were included in the study.

Ten consecutive single kidney patients (7 men), mean age 61.2 years (range 41–79), were examined. Unilateral nephrectomy had been performed in 6 patients between 1 and 32 years (mean 12.2) before admission for non-malignant renal disease. Two patients had unilateral renal agenesis and 2 had a contralateral rudimentary kidney *in situ*, having been non-functioning without symptoms for 3 and 32 years. All had uncomplicated stones in the renal pelvis and calices with a stone burden less than 3 cm in diameter.

As part of renal physiological studies (Karlsen and Berg, 1990), inulin clearance ($C_{IN}$) studies were performed the day before and the day after ESWL (at 24–32 h). Two 24-h urine collections were sampled before treatment (3 days and 2 days before) and 2 after treatment (0–24 and 32–56 h).

The patients were deprived of food and water from 12 pm the day before ESWL. Intravenous infusions of 1000 ml 5% glucose and 1000 ml normal saline were administered for 2 h during and after treatment; thereafter unlimited oral fluids were allowed. The patients were premedicated with pethidine 1 mg/kg. During treatment, small doses of intravenous analgesics and sedatives were administered as required (mean 0.10 mg phentanyl and 1.30 mg benzodiazepine).

ESWL was performed by the modified Dornier HM3 lithotriptor (Graff *et al.*, 1987) to 5 right-sided and 5 left-sided kidneys. The mean number of shocks was 2870 (range 2000–3500) delivered at 18 to 20 kV. The mean duration of water immersion was 25.4 min (range 15–35), the water temperature being constant at 37°C.

### *Analytical methods*

Urine samples were kept frozen at −20°C without preservatives until analysed. Freezing has been shown to have no adverse effects on the urinary GAG assay. Urinary excretion of GAGs was measured according to Whiteman (1973) after precipitation with Alcian blue. Aliquots of the 24-h urine samples were mixed with a buffered solution of Alcian blue containing magnesium chloride and left at room temperature overnight. The complex formed by the dye and urinary glycosaminoglycans was separated by centrifugation and dissociated in a solution of 7.5% sodium lauryl sulphate. The optical density of the Alcian blue was measured spectrophotometrically at 620 nm. Urinary excretion of GAGs was expressed as µg/min, the within assay coefficient of variation being 4.7%. The values in healthy human controls were 70.9 ± 15.6 µg/min (mean ± 1SD).

The Whiteman (1973) assay measures total urinary GAGs, including heparan sulphate, uronic acid, ribonucleic acid and chondroitin sulphate. Tamm-Horsfall mucoprotein from the kidney also forms complexes with Alcian blue, but their contribution to the GAG levels quantified by the Whiteman assay is unlikely to be significant.

Inulin concentrations were determined by means of the resorcinol reaction, *i.e.* hydrolysis of inulin to fructose by heating (Schreiner *et al.*, 1950).

The mean of the values obtained in the control periods before (3 in the animals, 2 in the patients) and the treatment periods after shock waves (4 in the animals, 2 in the patients) in each case was calculated. The mean and standard error of the mean (SEM) before and after the administration of shock waves was calculated, in the animals for both the exposed and non-exposed side. The values obtained before and after shock waves were compared statistically, as were the differences in reaction between the exposed and non-exposed side in the animals. Statistical comparisons were performed by the 2-tailed Wilcoxon signed rank test.

## Results

### *Animals*

There was a significant increase in urine volume after shock waves from both kidneys (Table 1). A significant increase in mean values of urinary excretion of GAGs occurred on both sides after administration of shock waves, more marked on the exposed side. There was no significant difference in response between the 2 sides. Urinary GAGs were increased throughout the observation time (4–5 h) on the exposed side; on the control side, baseline values were reached at the end of the observation period (Fig.). The glomerular filtration rate (GFR) measured as $C_{IN}$ remained unaltered in the exposed kidney but increased significantly in the contralateral kidney ($P < 0.01$) following exposure to shock waves (Table 1).

### *Patients*

Mean diuresis increased significantly after treatment ($P < 0.05$) (Table 2). Before ESWL, the urinary excretion of GAGs varied from 34.1 to 114.9 µg/min (mean 63.8 ± 6.1). The mean urinary GAG levels were unchanged after ESWL (Table 2). Mean urinary GAG excretion 0 to 24 h and 32 to 56 h after ESWL was 66.9 ± 8.1 and 62.2 ± 9.9 µg/min respectively. There seemed to be no correlation between stone localisation (pelvis or calix) and the values observed. In kidneys receiving less than 3000 shocks (n = 4) there was a fall in mean urinary excretion values from 58.4 ± 6.2 before to 50.3 ± 10.0 µg/min after treatment, while kidneys exposed to 3000 or more shocks (n = 6) showed an increase from 67.5 ± 9.5 to 78.0 ± 9.6 µg/min.

$C_{IN}$ was reduced from 66.4 ± 4.3 before to 61.0 ± 3.3 ml/min after ESWL ($P < 0.05$).

## Discussion

The exact origin of urinary GAGs is unknown, but they probably result from several processes such as

**Table 1** Changes in Urine Volume (UV), Urinary Excretion of GAGS and Inulin Clearance after the Administration of Shock Waves to 1 Kidney in 9 Dogs (see Methods)

| | *Exposed* | | *Non-exposed* | |
|---|---|---|---|---|
| *Parameter* | *Before* | *After* | *Before* | *After* |
| UV (ml/min) | 2.0 ± 0.2 | 2.6 ± 0.5* | 1.6 ± 0.2 | 2.4 ± 0.3* |
| GAGs (µg/min) | 61.3 ± 5.2 | 98.8 ± 12.0† | 60.5 ± 5.7 | 71.8 ± 4.9* |
| $C_{IN}$ (ml/min) | 27.9 ± 1.6 | 30.0 ± 2.8 | 26.6 ± 1.3 | 36.2 ± 2.4† |

Mean ± SEM.
* $P < 0.05$. † $P < 0.01$.

**Table 2** Urinary Volume, Urinary Excretion of GAGs and $C_{IN}$ before and after ESWL in 10 Patients with Single Kidneys (see Methods)

| *Parameter* | *Before* | *After* |
|---|---|---|
| UV (ml/min) | 1.0±0.1 | 1.6±0.1* |
| GAG (μg/min) | 63.8±6.1 | 64.5±7.8 |
| $C_{IN}$ (ml/min) | 66.4±4.3 | 61.0±3.3* |

Mean±SEM.
* $P<0.05$.

tissue breakdown and release, glomerular filtration and tubular reabsorption. Urinary excretion of GAGs has been found to correlate with GFR (Newton *et al.*, 1979). There is also evidence that urinary GAGs may be secreted by the urothelium along the urinary tract (Thorne and Resnic, 1984) and there is a decrease in urinary GAGs following removal of the GAG-mucin layer. Cystectomy does not, however, result in qualitative or quantitative changes in the excreted GAGs (Hurst *et al.*, 1987), indicating that most of the normal urinary GAGs originate from the kidney. GAGs are filtered from the plasma to urine by the glomerulus (Shum *et al.*, 1984) and the kidney membranes have been found to contain surface proteoglycans in high concentrations (Stow *et al.*, 1985).

After damaging the mucin layer of the rat bladder urothelium experimentally with weak acids, there is a momentary increase in the concentration of GAGs in bladder washings (Grenabo *et al.*, 1988). During induced infection in the rat bladder, the GAG layer was seen by scanning electron microscopy to slough off as part of the tissue injury (Balish *et al.*, 1982). In rabbits, full regeneration of the urothelial mucosal layer occurs within 24 h of destruction by weak acids (Parsons *et al.*, 1977). Following induced cystitis in monkeys, urinary excretion levels increased as infection developed and returned to baseline levels as the infection resolved (Uehling *et al.*, 1988). Injury to the GAG/mucin layer by any agent therefore probably induces a momentary increase in the urinary excretion of GAGs.

In the present animal study, a significantly increased level of urinary excretion of GAGs was observed immediately after unilateral administration of extracorporeal shock waves to the renal pelvis, more pronounced on the exposed side. It may reflect damage to the GAG/mucin layer covering the pelvic urothelium, release of GAGs from the injured renal tissue or increased glomerular filtration of GAGs. As there was no change in GFR in the canine kidneys exposed to the shock waves (Table 1), the significant increase in urinary excreted GAGs must reflect damage to the pelvic urothelium or renal tissue.

Single kidney patients should be an ideal model for detecting alterations in urinary excretion of GAGs after ESWL. In the present study, however, the results in the patients did not reflect the changes observed in the animals. A possible explanation may be the small fall in GFR detected in the patients the day after treatment (Table 1). In addition, the urine tested was from the 24-h urine collections sampled during the 0–24 and 32–56 h periods after ESWL and the increase in urinary excretion of GAGs following tissue injury is likely to be short-lived. Testing the urine immediately after ESWL, as we did in the animal experiments, might possibly detect a change in patients as well. The data may suggest a higher urinary excretion of GAGs after more than 3000 shock wave exposures.

It was concluded that extracorporeal shock waves increase the urinary excretion of GAGs in dogs 4 to 5 h after exposure. The increase probably reflects uroepithelial or renal tissue injury. No such increment was detected in the patients.

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# Upper Tract Tumours following Cystectomy for Bladder Cancer. Is Routine Intravenous Urography Worthwhile?

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Summary—The incidence and presentation of upper tract tumours were studied in 180 patients who had previously undergone cystectomy for transitional cell carcinoma of the bladder. Intravenous urography was performed routinely 3 months after cystectomy, 1 year later and at 3-yearly intervals thereafter. Ten patients developed upper tract tumours; 1 presented with loin pain and the remainder with haematuria.

Six patients underwent nephroureterectomy and 5 of them lived for at least 4 years; 4 were inoperable and only 1 survived longer than 6 months.

In this series, all patients with upper tract tumours presented with symptoms and routine intravenous urography failed to detect any asymptomatic lesions. Routine radiological assessment of the upper tracts to detect tumours is not justified following cystectomy.

Cystectomy and ileal loop diversion have an established place in the management of patients with transitional cell carcinoma of the bladder. Transitional cell carcinoma is often multifocal and these tumours may also involve the renal pelvis, ureter and urethra (Kaplan *et al.*, 1951). This has been attributed to seeding of exfoliated cells (Boreham, 1956) and the entire urothelium may be sensitive to carcinogenic stimuli (Schellhammer and Whitmore, 1976).

The incidence of upper tract transitional cell tumours in patients who have had bladder cancer is reported as 5.9% (Mateos *et al.*, 1987). However, 40 to 54% of patients presenting with renal transitional cell tumours will develop a bladder lesion (Walzer and Soloway, 1983).

Patients who have had their bladders removed for transitional cell carcinoma are therefore at risk of subsequently developing upper tract tumours. The aim of this study was to quantify this risk and assess the value of routine post-operative urography in detecting such disease in a single unit with a large experience of cystectomy.

## Patients and Methods

The study group comprised 180 patients (148 men, 32 women), all of whom had undergone cystectomy and ileal loop diversion for transitional cell carcinoma of the bladder between 1969 and 1989. In addition to regular follow-up with physical examination and biochemical assessment of renal function, all patients undewent intravenous urography (IVU) 3 months after surgery, 1 year later and at 3-yearly intervals thereafter. Additional IVUs and further investigations such as ultrasound, loopograms and antegrade studies were performed as indicated clinically. The case notes of all patients were studied retrospectively to determine the incidence of upper tract tumours in this group, with particular emphasis on how these tumours presented and the value of routine urography.

The $\chi^2$ test was used for statistical analysis.

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

## Results

The mean age of the patients was 65 years (range 34–77). The indications for cystectomy are shown in Table 1.

Sixteen patients died within 3 months of surgery and the remainder had at least 1 post-operative IVU.

### *Incidence and presentation of tumours*

In all, 10 patients developed upper tract lesions and these occurred between 1 and 9 years after cystectomy (mean 3.8). None of these tumours was detected on routine follow-up urography; in 9 of the 10 patients an IVU was performed after they reported haematuria. All had undergone an IVU which was considered normal between 6 months and 30 months previously. The remaining patient had an IVU at the planned time (3 years after the previous study); however, this cannot be considered an asymptomatic presentation because he was admitted to the unit as an emergency with left loin pain and was found to have a tumour in the left renal pelvis.

In addition to the 9 patients in whom a tumour was found after they noted haematuria, a further 16 reported blood in the urine. Despite full investigation, only 1 man, who had a staghorn calculus, was found to have any significant pathology to account for the haematuria. The site of the upper tract tumours is shown in Table 2. Four patients had more than 1 lesion. In 6 cases the diagnosis was made by IVU alone; 3 required loopograms and the remaining patient also had an antegrade pyelogram.

**Table 1** Indications for Cystectomy

| *Indication* | *No.* |
|---|---|
| Uncontrollable superficial disease | 59 |
| Invasive disease (with pre-operative radiotherapy) | 58 |
| Salvage cystectomy (after radical radiotherapy) | 52 |
| Carcinoma *in situ* | 11 |

**Table 2** Site of Upper Tract Tumours

| *Site* | *No.* |
|---|---|
| Renal pelvis | 10 |
| Upper ureter | 2 |
| Lower ureter | 4 |

(Four patients had multiple tumours).

### *Treatment*

Six patients were considered operable and all underwent nephroureterectomy. Of this group, 3 were alive 4 to 10 years after nephroureterectomy and the 3 who died lived for 1, 4 and 7 years after surgery before dying of recurrent disease. Four patients were considered inoperable, including 1 man who had undergone a nephroureterectomy elsewhere prior to cystectomy; 3 of this group died within 6 months of diagnosis of the upper tract tumour. The remaining patient had bilateral renal pelvic tumours. He was treated with monthly instillations of Epodyl (triethylene glycol diglyceridyl ether; 20 ml of a 20% solution) into his loop and lived for a further 4 years. Although there was a regression of the tumours as judged by serial IVUs, the lesions did not resolve completely.

### *Histopathology*

The incidence of upper tract tumours was compared with the previous bladder histology in these patients (Table 3). Of the 10, 7 had pT1 bladder disease, 2 had pT2 lesions and the remaining patient had pT3 disease; 4 of the 10 also had evidence of carcinoma *in situ* (CIS).

There was a significantly greater incidence of upper tract tumours in the group with previous non-invasive bladder disease (11.9%) compared to those with invasive tumours (2.7%). Although upper tract tumours were commoner in patients who had additional areas of CIS in the bladder, when compared to those without such changes, there was no statistical difference. The histology of the cut end of the ureter in the original cystectomy specimens showed that the appearances were normal in 9 of these patients. The remaining patient was noted to have dysplastic epithelium which fell

**Table 3** Incidence of Upper Tract Tumours in Relation to Bladder Tumour Stage and Presence of Areas of Carcinoma in situ

| *Stage* | *Total* | *No. of upper tract tumours (%)* |
|---|---|---|
| pTa, pT1 | 59 | 7 (11.9)* |
| pT2, pT3 | 110 | 3 (2.7)* |
| CIS present | 50 | 4 (8.1)† |
| CIS absent | 130 | 6 (4.6)† |

* $0.05 > P > 0.01$.
† Not significant.

short of the criteria for CIS. He later developed a lower ureteric tumour.

Histology of the nephroureterectomy specimens revealed 1 patient with a well differentiated lesion and 1 with a poorly differentiated tumour. The remainder were considered moderately differentiated. Only 1 case did not show invasion.

## Discussion

The incidence of upper tract tumours in patients who had previously undergone cystectomy has been reported to be as low as 3.3% by Zincke *et al.* (1984). Mufti *et al.* (1988) found the incidence to be higher at 8.5% and both groups suggested that careful follow-up of the upper tracts was mandatory. Whilst our incidence (5.5%) is of the same order as these other studies, follow-up with regular IVUs has not been helpful since all of the patients with upper tract tumours presented with symptoms.

Regular urinary cytology of loop specimens has been proposed as another method of follow-up of post-cystectomy patients (Soloway, 1984). We have not found it to be of value, with 3 false negative results in the 3 patients so investigated.

It is clear that haematuria in post-cystectomy patients is a significant symptom, since over one-third of our patients with bleeding were shown to have renal pelvic or ureteric tumours. Where applicable, surgical treatment has proved very rewarding. Nephroureterectomy is the operation of choice (Mufti *et al.*, 1988) and 5 of our 6 patients so treated survived for more than 4 years. The satisfactory result of Epodyl instillations in 1 of the patients with bilateral disease suggests that this form of treatment can be helpful in inoperable cases provided that free reflux is present.

The incidence of upper tract tumours was greater in those patients with non-invasive disease of the bladder. Whilst this may reflect the nature of the tumour, it should be noted that 71% of those with non-invasive disease were alive 3 years after cystectomy compared to 40% of those with muscle-invasive tumours. This finding may have an effect in the difference in incidence of upper tract tumours in the 2 groups.

Linker and Whitmore (1975) demonstrated an 8.8% incidence of CIS in the cut end of the ureter in cystectomy patients but found that this group did not appear to be at greater risk of the later development of upper tract tumours. In the present study, the distal end of the ureter appeared normal in 9 of the 10 patients with tumours.

Routine post-operative urography was undertaken in the expectation of detecting upper tract tumours at a pre-clinical stage, in the hope of improving the outcome. We have performed more than 400 IVUs and we have not detected a single asymptomatic tumour. It is concluded that with the exception of an early study to check drainage of the upper tracts following surgery, post-cystectomy IVUs should be reserved for those patients with symptoms.

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# Transitional Cell Carcinoma of the Upper Urinary Tract: Prognostic Variables and Post-operative Recurrences

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Summary—In a retrospective study of 198 patients with transitional cell carcinoma of the upper urinary tract, post-operative recurrences developed as contralateral tumours in 2.5%, in the ureteric stump after conservative resection in 19% and in the bladder in 36.4%. Upper tract recurrences resembled the primary tumours in terms of grade and stage; of the bladder tumours, 89% were similar in grade and 72% similar in stage to the primary tumours.

Age, sex, grade and stage had no effect on the number of bladder recurrences, but ureteric tumours had significantly more recurrences than renal pelvicaliceal tumours. Sex, bladder recurrences and site of primary tumours did not influence survival. Thus grade and stage of the primary tumour were the only predictive variables of the final outcome.

Transitional cell carcinoma (TCC) of the upper urinary tract is an uncommon disease that accounts for approximately 6 to 8% of all upper tract and urothelial tumours (McCarron *et al.*, 1983; Huben *et al.*, 1988).

The various parts of the urinary tract form a coherent whole and due to the fact that coexistence of widespread dysplasia has been demonstrated (Auld *et al.*, 1984; Kakizoe *et al.*, 1980) and that bladder tumours in many respects behave like tumours of the upper urinary tract (Kvist *et al.*, 1988), follow-up is needed to detect further tumour development in the remaining urothelium. Earlier studies have shown subsequent contralateral tumours in up to 9% of patients (Hatch *et al.*, 1988; Kirkali *et al.*, 1989), ipsilateral tumours in about 22% after local resection (Mufti *et al.*, 1989), ureteric stump recurrences in 15 to 64% of nephrectomy and partial nephro-ureterectomy (Kakizoe *et al.*, 1980; Kirkali *et al.*, 1989) and bladder tumours in 18 to 48% (Kakizoe *et al.*, 1980; Mufti *et al.*, 1989). Although follow-up may include cytology of the urine and ultrasound examination of the bladder, cystoscopy remains the conventional means of detecting bladder tumours, with intravenous urography and pyelography used in the case of pelvicaliceal and ureteric tumours. Endoscopic monitoring is time-consuming, expensive and inconvenient for patients, but necessary as long as no effective adjuvant radiotherapy or chemotherapy can be offered (Huben *et al.*, 1988; Mufti *et al.*, 1989).

The intervals between post-operative endoscopic checks must be based upon data showing the likelihood of consistency between grades of dysplasia and invasive potential among primary and secondary tumours; estimates of time-related risks for the latter are mandatory. We have examined our records over the last 22 years in order to define prognostic factors that could affect the number of recurrences or survival following TCC of the upper urinary tract.

## Patients and Methods

A total of 280 patients were treated for TCC of the upper urinary tract between 1965 and 1987. For a variety of reasons (age, physical debility, advanced disease, removal to other areas, other concurrent neoplasm or death), no follow-up was done in 82 cases. This left 198 patients (median age 68 years, range 42–88) for evaluation. Surgical procedures

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included 9 nephrectomies, 28 partial nephro-ureterectomies and 129 nephro-ureterectomies with excision of cuff of bladder. Local resections were performed in 32 patients as the only procedure and in 2 cases due to bilateral involvement. In the observation period 3 patients underwent radical cystectomy.

Follow-up (mean 46 months, range 3–240) include cystoscopy every 3 months regardless of stage and grade, although the intervals were gradually increased until no recurrence had been demonstrated over the course of 5 years. If ureteric or pelvicaliceal tumours were suspected, cytology of the urine, intravenous urography and retrograde pyelography were done. Data concerning the status of the patients were provided by the National Register; 124 patients died during the study period.

Dysplasia (grades O–IV) was classified according to Bergkvist *et al.* (1965). Grades I and II represented low grade tumours and grades III and IV represented high grade tumours. Grade I corresponds to Grade I (WHO), Grade II to Grade II (WHO) and Grades III and IV to Grade III (WHO) in the 1973 WHO classification (de Voogt *et al.*, 1979).

Staging was done according to the TNM classification (UICC, 1978). Tumours infiltrating the subepithelial connective tissue were considered invasive.

### *Statistical methods*

Tumour recurrence rates according to age, sex, grade or dysplasia, stage and location were analysed using Fisher's exact test (1 d.f.). Survival and description of the first post-operative bladder tumour were calculated using Kaplan and Meier's life-table method.

Comparison of survival rates was based on the log-rank test (d.f. = no. of groups − 1).

Unless otherwise indicated, intervals (percentages) in brackets represent the 95% confidence limits (binomial).

A 5% level of probability ($P<0.05$) was chosen for statistical significance.

## Results

The distribution of primary tumours at diagnosis in relation to age and sex is shown in Figure 1. Males (n = 122) outnumbered females (n = 76), the sex ratio being 1.6:1.

At referral the primary TCCs of the upper urinary tract were located in the pelvis in 115 patients (64 on the right side and 51 on the left) and in the ureter in 64 (43 right, 21 left); 19 were multifocal (either ipsilateral (17) or bilateral (2)). In 126 patients the tumours were low grade (I + II) and in 72 they were high grade (III + IV). No difference was found between the sexes ($P>0.38$) (Table).

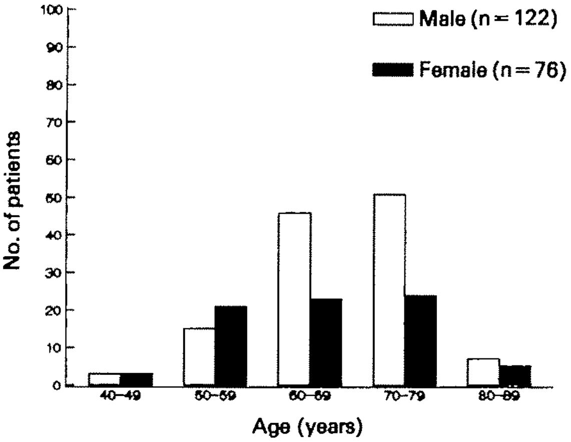

**Fig. 1** Mean age at presentation.

Ninety-three patients had non-invasive tumours (pTa), 29 had invasion of the lamina propria (pT1) and in 76 patients the invasion penetrated the muscular layer or deeper (pT2–4). The distribution between the sexes was equal ($P>0.95$) (Table). Fifteen of 19 multifocal tumours (79%) were invasive compared with 90 of 179 solitary tumours (50%) ($P<0.03$).

### *Recurrences*

Contralateral ureteric or pelvic tumours occurred synchronously in 2 patients (1%; 0.1–3.6%) and subsequently in 5 (2.5%; 0.8–5.8%) from 5 to 8 years after surgery. Nephrectomy and partial nephro-ureterectomy (n = 37) were complicated by ureteric stump recurrences in 7 patients (19%; 8–35.2%) from 3 months to 4 years after surgery; 2 of these were low grade invasive, 2 high grade invasive and 3 low grade non-invasive.

Of the patients treated by local resection only (n = 32), 3 (9%; 2–25%) had ipsilateral recurrences

**Table** Distribution of Grades and Stages

| | *Low grade (I+II)* | | *High grade (III+IV)* | | *Non-invasive* | | *Invasive* | |
|---|---|---|---|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Female | 45 | 52 | 31 | 48 | 35 | 46 | 41 | 54 |
| Male | 81 | 72 | 41 | 28 | 58 | 48 | 64 | 52 |

after 1 to 5 years; 2 of these were high grade invasive and 1 low grade non-invasive. In all upper tract recurrences the grading and staging were the same as for the primary tumour.

In 72 patients (36.4%; 29.7–43.5%) the bladder tumour appeared from 0 to 14 years post-operatively and 4 of these (2%; 0.6–5.1%) were concurrent. A further 17 (8.6%; 5.1–13.4%) also had preceding bladder tumours and 51 (25.8%; 19.8–32.4%) had only subsequent bladder tumours.

Age (below or above 65 years) did not seem to influence bladder tumour recurrences ($P>0.32$). While a male predominance was found at presentation, no difference between the sexes and subsequent bladder tumours could be found ($P=1.00$).

The site of the upper tract TCCs had a major influence on recurrence rates, with ureteric tumours having significantly more recurrences ($P=0.04$) than pelvic tumours irrespective of the type of treatment. This could not be demonstrated among patients undergoing total nephro-ureterectomy including a cuff of bladder for solitary tumours ($P>0.15$). Ten of the 19 patients (53%) with multifocal tumours had recurrences compared with 62 of the 179 (35%) with solitary tumours ($P<0.20$).

In 64 patients (89%; 79.3–95%) the grades of the bladder tumours were similar to those of the TCCs of the upper urinary tract. Five tumours (7%) changed from low to high grade and 3 (4%) became lower. Although a higher percentage (39%) of high grade than low grade tumours (35%) had recurrences, the difference was not significant ($P>0.68$). The risks of developing a subsequent bladder tumour in relation to grades of dysplasia are shown in Figure 2.

In 52 patients (72%; 60.4–82.1%), staging of the bladder tumours was equal to that of the TCCs of the upper urinary tract. Sixteen patients (22%) with primary invasive upper tract TCCs had subsequent non-invasive bladder tumours and 4 non-invasive tumours (6%) became invasive. Although without statistical significance ($P>0.69$), the invasive tumours had a higher recurrence rate (38%) than non-invasive tumours (34%). The risk of a subsequent bladder recurrence in relation to the invasive potential is shown in Figure 3.

### *Survival*

No differences were found in survival between males and females ($P=0.10$) (Fig. 4) or between patients with and without bladder recurrences ($P>0.37$) (Fig. 5). Location (pelvis, ureter or multifocal) had no effect on survival ($P>0.20$) (Fig. 6). Major differences were found between low and high grade tumours ($P<0.0001$) and between invasive and non-invasive tumours ($P<0.006$) (Fig. 7).

## Discussion

Concurrent contralateral tumours (1%) and subsequent contralateral recurrences (2.5%) were rare and the recurrences occurred later than the normal control period. Annual medium contrast imaging after TCC of the upper urinary tract has been proposed because of the high recurrence rate (Hatch *et al.*, 1988). However, a number of series (Murphy *et al.*, 1980; Murphy *et al.*, 1981; Kirkali *et al.*, 1989; Mufti *et al.*, 1989), including the present study, have shown a very low contralateral recur-

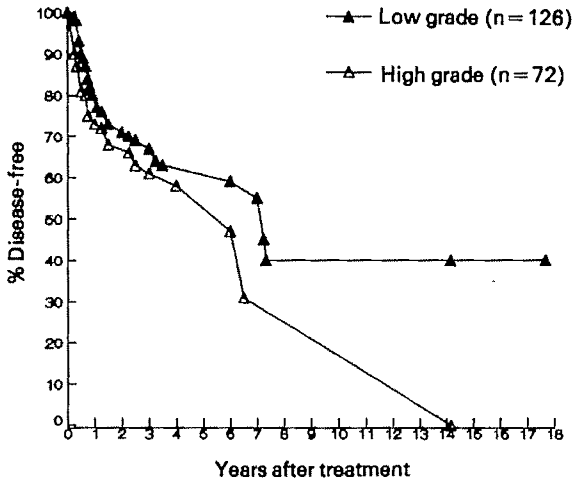

**Fig. 2** Bladder recurrence and grade.

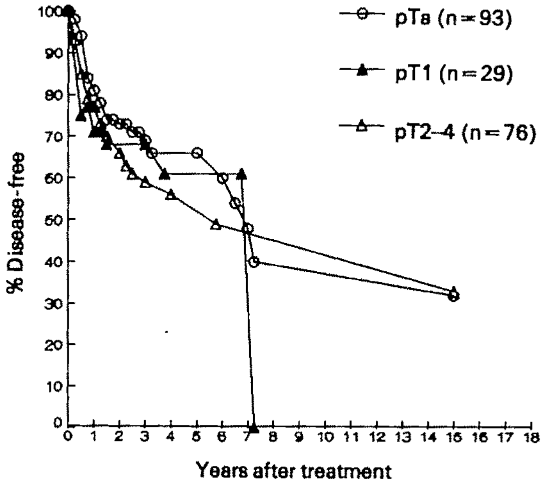

**Fig. 3** Bladder recurrence and stage.

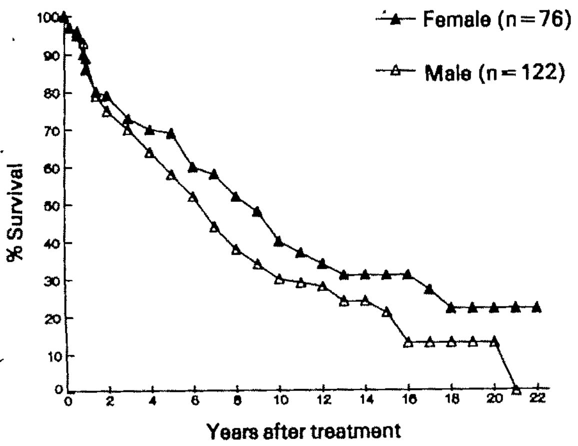

**Fig. 4** Survival and sex.

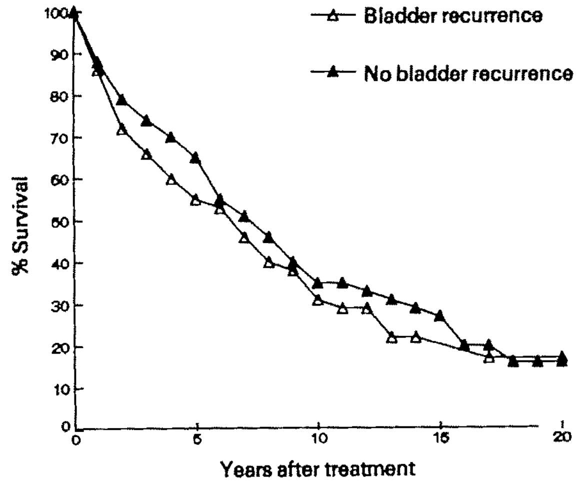

**Fig. 5** Survival and bladder recurrence.

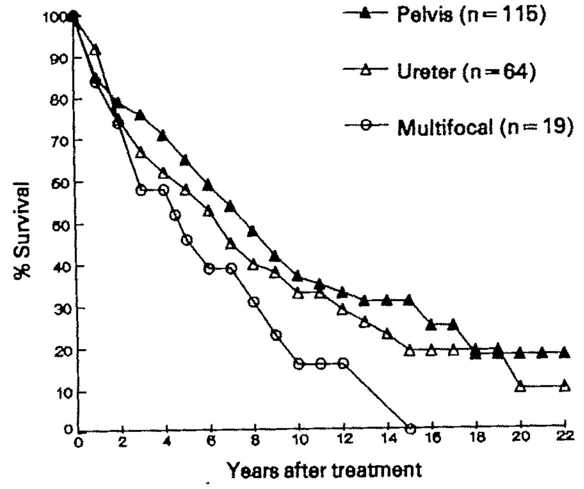

**Fig. 6** Survival and location of primary tumour.

rence rate (1.5–2.5%) and we do not recommend this procedure.

Our ureteric stump recurrence rate was lower than in some series (Kakizoe *et al.*, 1980; Mufti *et al.*, 1989) but was in accordance with the findings of Kirkali *et al.* (1989). No criteria were found to predict upper tract recurrence.

The total number of bladder recurrences resembled that found in other studies. Tumour differentiation remained fairly consistent, both temporally and spatially, in accordance with the study of Booth *et al.* (1980). Minor differences were due to intra- and inter-observer variations.

A greater difference was found in staging, as 16% of patients with primary invasive tumours had subsequent non-invasive bladder tumours. We believe that this was partly due to the inherent weakness of the basic biopsy, a pathological sample yielding less information than the total resected specimen. The true percentage of similarity must be higher. As with bladder cancer, therefore, most TCCs of the upper urinary tract must be considered to have consistent invasive potential and grades of dysplasia at recurrence.

It is clear from Figures 2 and 3 that the actual risk of developing bladder recurrences is only slightly affected by grade and stage. The slope of the curves indicates that the highest risk occurs during the first 2 years, although a first recurrence was seen 14 years after treatment.

Age and sex had no predictive value with regard to recurrence rates. Surprisingly, bladder recurrence did not affect survival. Whether this was a result of close surveillance and prompt treatment could not be assessed from this study.

Ureteric tumours had a significantly higher number of recurrences, in contrast to the study of Zincke and Neves (1984), but again without influencing survival (Kirkali *et al.*, 1989; Mufti *et al.*, 1989).

Sex ought to be a predictor of survival; a trend was found ($P=0.10$) and may be explained by the well known difference in the general population, a difference that cannot be demonstrated with this sample size. Kirkali *et al.* (1989) found that females had a worse prognosis than males as a result of more extensive tumours at presentation. We found no differences at referral between invasive potential and grades in males and females and thus no difference in survival.

In conclusion, the only prognostic variable with an increased number of recurrences was the site of the primary tumour in the ureter. Dedifferentiation and invasive potential were the only variables

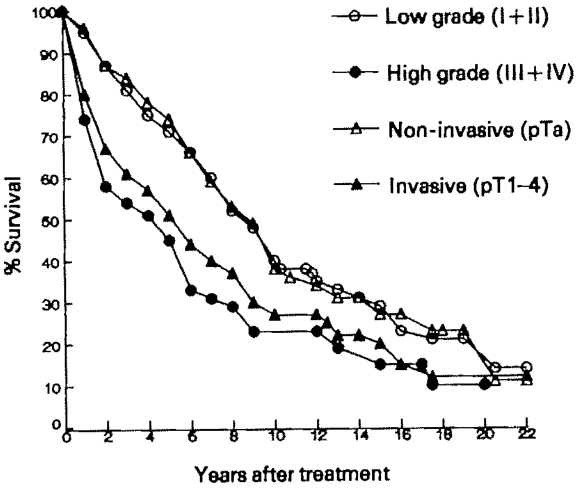

**Fig. 7** Survival and tumour grade and stage.

affecting survival. Others have found that multifocal tumours increased the recurrence rate and worsened the prognosis (Booth *et al.*, 1980; Mufti *et al.*, 1989). We were unable to confirm this, possibly because of the small number of multifocal tumours.

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# Pattern of Urological Malignancy in Zambia

## A Hospital-based Histopathological Study

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Summary—The pattern of urological malignancy among the indigenous population of Zambia (determined on the basis of histopathological reports from a major national hospital during an 8-year period) is presented. A total of 6514 malignancies were observed, of which 784 (12%) were of urological origin. Bladder carcinoma, predominantly squamous type, was the commonest urological tumour (51%), followed by carcinoma of the prostate (26%), carcinoma of the penis (18%), renal tumours (4.3%) and testicular malignancy (0.7%). In nearly 32% of the bladder tumours, bilharzial ova were demonstrated histopathologically. Nephroblastoma accounted for 70% of the renal tumours and from a total of 7 cases of testicular tumours 5 were embryonal carcinoma and 2 seminoma. A brief reference is made to the pattern and aetiology of urological malignancies in some neighbouring countries.

The incidence of cancer has a wide geographical variation and a sound knowledge of its prevalence at both national and international levels is important. Investigations into the geographical variation of a neoplasm may provide vital information on its aetiology, while the absence of adequate information at a national level is likely to hinder the effective planning of a health service. Statistical investigations of neoplastic disorders are usually based on the incidence of mortality and newly diagnosed cases, but in many third world countries these figures are not readily available. Valid information may, however, be obtained from alternative sources. We present an account of the pattern of urological malignancy in Zambia compiled from the histopathological reports of a major national hospital.

### Materials and methods

Zambia is a sub-Saharan African country with a population (recorded during the last census in 1980) of slightly more than 5.5 million. The University Teaching Hospital, located in the capital city of Lusaka, acts as the national referral centre and receives surgical specimens from the entire country, excluding the mining province of the Copperbelt (Fig. 1) with a population of 1.25 million. The mines and major government hospitals in the province have their own histopathological services. The information now presented, in the absence of a population-based cancer registry, has been compiled from analysis of histopathological reports from the University Teaching Hospital during an 8-year period (1980–1987).

### Results

During the stated period 6514 malignancies were reported; 784 of these (12%) were of urological origin (Table 1). Bladder tumour was the most common urological tumour (51%) followed by carcinoma of the prostate (26%), carcinoma of the penis (18%), renal tumours (4.3%) and testicular neoplasms (0.7%). Bladder and prostatic malignancies were the only 2 urological tumours to be included in the top 10 malignant disorders of the country (Table 2). Most of the bladder tumours were squamous carcinoma, with bilharzial ova demonstrated histopathologically in approximately 32% (Table 3). More than half of the patients were below the age of 50 years and 50% were less than 40. Histologically, all prostatic malignancies were

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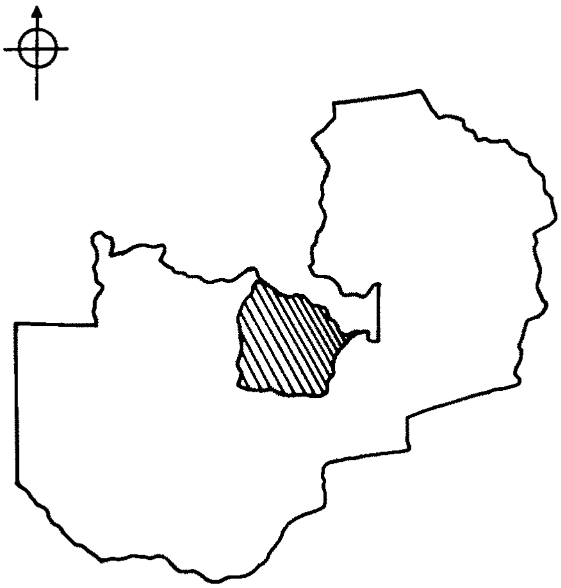

**Fig. 1** Map of Zambia. Surgical specimens were received from the entire country excluding the shaded area.

adenocarcinoma; according to Gleasson's classification, 80% were between grades 3 and 5; nearly 55% of the patients were less than 64 years old (Fig. 2) and 5% of the specimens contained bilharzial ova. Of the renal tumours, nephroblastoma accounted for 70% and of 7 testicular neoplasms 5 were embryonal carcinoma and 2 seminoma.

## Discussion

Carcinoma of the bladder was the most common urological tumour in Zambia. The preponderance of squamous carcinoma in a relatively young age group, as observed in the present study, has also been reported in a large number of African countries with endemic bilharziasis (Attah and Nkposong, 1976; Bhagwandeen, 1976; Hicks *et al.*, 1982), thus giving credence to the suspected causal role of the parasite. Carcinoma of the prostate was the second most common tumour and is known to occur frequently in East, West and South African Blacks (Nkposong *et al.*, 1987). However, the high incidence in Zambia, despite the presence of only a limited number of octogenarians, is significant. The absence of ritual circumcision in the majority of Zambian tribes, coupled with a poor standard of personal hygiene, has contributed towards the high incidence of penile cancer. The above factors, plus others, have been incriminated in its aetiology in

**Table 1** Site of Tumour and Average Age of 784 Patients with Urological Malignancies

| *Organ* | *No. of patients (%)* | *Average age (years)* | *% in relation to all tumours* |
|---|---|---|---|
| Bladder | 398 (50.9) | 48 | 6.10 |
| Prostate | 205 (26.2) | 62 | 3.11 |
| Penis | 140 (17.90) | 49 | 2.14 |
| Kidney | 34 (4.3) | | 0.52 |
| Wilms' tumour | 24 | 4 | |
| Adenocarcinoma | 10 | 44 | |
| Testis | 7 (0.7) | | 0.10 |
| Embryonal carcinoma | 5 | 3 | |
| Seminoma | 2 | 35 | |

**Table 2** Commonest Malignant Disorders in Zambia Observed between 1980 and 1987

| *No.* | *Sites* | *Total no. (%)* |
|---|---|---|
| 1 | Cervix | 1148 (17.6) |
| 2 | Skin (excluding Kaposi's sarcoma) | 625 (9.6) |
| 3 | Soft tissue (including Kaposi's sarcoma) | 548 (8.4) |
| 4 | Lympho-reticular | 439 (6.7) |
| 5 | Bladder | 398 (6.1) |
| 6 | Liver (primary) | 364 (5.6) |
| 7 | Breast | 268 (4.1) |
| 8 | Prostate | 205 (3.1) |
| 9 | Stomach | 178 (2.7) |
| 10 | Eye | 177 (2.7) |
| 11 | Oesophagus | 172 (2.6) |
| 12 | Colorectal | 161 (2.4) |
| 13 | Penis | 140 (2.1) |
| 14 | Oropharynx | 122 (1.8) |
| 15 | Lung | 96 (1.4) |
| 16 | Larynx | 93 (1.4) |
| 17 | Maxillo-facial | 89 (1.3) |
| 18 | Corpus uteri | 85 (1.3) |
| 19 | Ovary | 76 (1.1) |
| 20 | Vulvo-vaginal | 76 (1.1) |
| | Total | 5460 (83.1) |

**Table 3** Features of 398 Cases of Bladder Carcinoma

| *Histological type* | *No. (%)* | *M:F ratio* | *Average age (years)* | *No. of cases with ova (%)* |
|---|---|---|---|---|
| Squamous | 281 (70.6) | 1.01:1 | 50 | 95 (33.8) |
| Transitional | 75 (18.8) | 1:1 | 50 | 19 (25.3) |
| Adeno | 22 (5.5) | 1.75:1 | 41 | 6 (27.3) |
| Anaplastic | 20 (5.0) | 1.05:1 | 45 | 5 (25) |

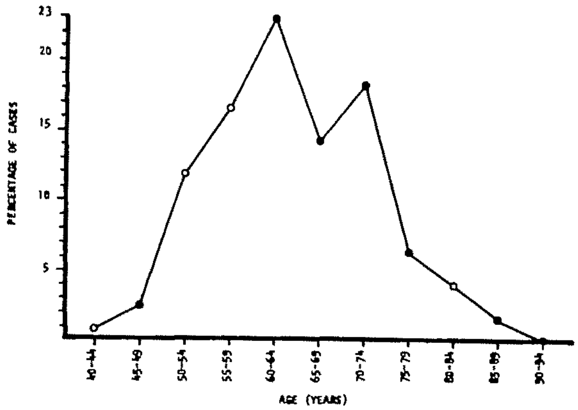

**Fig. 2** Age distribution of patients with prostatic carcinoma.

Uganda, where penile cancer is the most common male malignant disorder (Olweny, 1982). Compared with nephroblastoma, the relative infrequency of adenocarcinoma of the kidney has been reported from other sub-Saharan countries (Awori, 1975; Lawani *et al.*, 1982). The rarity of testicular tumours among the Black population in North America and Africa is well known (Mostofi and Price, 1973; Zimmerman and Kung'u, 1978). However, the incidence of untreated undescended testes in the adult population in Zambia appears rather high; an average of 6 such cases is annually seen by one of the authors (B.E.) in Lusaka alone. The infrequency of testicular tumours of germ cell origin in Zambians thus remains difficult to explain.

The absence of significant variation in tribal customs and climatic conditions in the country, together with the extensive catchment area of the University Teaching Hospital, make it reasonable to suggest that the information in this report is a fairly accurate representation of the pattern of prevailing urological malignancies in Zambia, though not necessarily of their incidence.

## Acknowledgements

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# Urodynamic Morbidity and Dysuria Prophylaxis

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Summary—A group of 324 patients received prophylactic treatment with either sodium bicarbonate, potassium citrate or a glucose placebo following urodynamic studies. Urine was screened for infection both before and after testing and the incidence of dysuria assessed by postal questionnaire; 63% of patients experienced some degree of dysuria and this was severe and prolonged in 6.3%, the majority of whom were male. Neither sodium bicarbonate nor potassium citrate was any more effective in preventing dysuria than placebo. The presence of severe prolonged dysuria was not associated with a urinary tract infection or with any particular urodynamic diagnosis.

Dysuria following urodynamic investigations is a common problem. In a previous study (Powell *et al.*, 1982), we showed that nearly 25% of all patients experienced some lower tract symptoms but only 1.5% of all patients acquired a urinary tract infection (UTI).

We have now reassessed the incidence of morbidity following urodynamic tests and attempted to reduce the level of dysuria by giving prophylactic treatment aimed at making the urine more alkaline.

## Patients and Methods

The study group included 324 consecutive patients, 89 male and 235 female. The only exceptions were patients still requiring an indwelling catheter following urodynamic tests, those undergoing urodynamics prior to undiversion or patients thought to be mentally incapable of complying with the protocol. A catheter specimen of urine (CSU) was taken at the start of the tests, which consisted of urethral pressure profilometry, filling and voiding cystometry, and also a simultaneous video study in 35% of cases. Following urodynamics, the patients were randomly allocated to 3 groups consisting of 48 hours' treatment with either sodium bicarbonate, potassium citrate, or glucose, each at a dosage of 5 g 4 times daily. Before leaving they were given a sterile Boricon urine container and instructions to provide a mid-stream specimen of urine (MSU) 24 h later. A stamped addressed box was supplied for the patients to return their sample.

Two days after the study, each patient received a postal questionnaire which he/she was asked to complete and return in a postage paid envelope. The questionnaire related to symptoms of dysuria or haematuria and their duration and severity. Patients were asked their opinion of the urodynamic tests and whether their family doctor had subsequently prescribed any treatment.

## Results

A total of 314 patients provided an MSU and 310 completed and returned the questionnaire, with 1 remainder being sent. Patients had been asked to describe their dysuria, if present, as either mild, moderate or severe and to give its duration as less than 24 h, 48 h, or 72 or more hours. Minimal dysuria was taken as mild and lasting 24 h or less and severe prolonged dysuria as lasting 72 h or more.

Some degree of dysuria was initially experienced by 63% of all responders, with a similar percentage

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Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

of males and females being affected (71% of males and 60% of females, $P>0.05$). Only 6.3% of all patients stated that they had severe prolonged dysuria following urodynamics but this consisted of a higher percentage of males than females (13.5% of males and 3.4% of females).

In all, 290 pre-test CSUs were examined and 25 patients (8.5%) were found to have infected urine ($>10^5$ organisms per high power field). However, only 3 of these 25 patients had a significant pyuria associated with this (>50 white cells per high power field) and so could be said to have a urinary tract infection.

Of the 314 patients returning the MSUs following urodynamics, 10% had infected urine and 3.1% (10/314) had UTI. Of this group, 5 patients were known to have had sterile urine at the time of the test and 1 had not had a CSU, so that our overall introduced infection rate was a maximum of 1.9%. None of the patients who complained of severe, prolonged dysuria had acquired a urinary tract infection following urodynamics.

Of the 27 responders who experienced haematuria, 25 also complained of some dysuria, 8 of them having severe prolonged dysuria; again, none of this group had acquired an infection.

A similar percentage of patients complaining of minimal dysuria was found in each treatment group (Table). However, patients who had been taking sodium bicarbonate had a significantly lower incidence of severe prolonged dysuria than those taking potassium citrate ($P=0.047$), although neither treatment appeared significantly more successful than the placebo in preventing dysuria ($P>0.05$).

Ten patients reported side effects. Two in the bicarbonate group complained of nausea only, whereas 8 patients taking potassium citrate complained of more severe side effects, including vomiting, diarrhoea and stomach cramps.

Seven patients reported that they had been put on antibiotics by their family doctor after complaining of significant dysuria following the urodynamic investigations. None had either UTI or infected urine before or after the tests had been performed.

**Table** Effect of Treatment on Dysuria

| *Treatment* | *Minimal dysuria No. of patients (%)* | *Severe prolonged dysuria No. of patients (%)* |
|---|---|---|
| Sodium bicarbonate | 64/110 (58) | 3/110 (0.9%) |
| Potassium citrate | 75/110 (68) | 10/110 (3.1) |
| Glucose (placebo) | 66/104 (64) | 7/104 (2.2) |

Analysis of the urodynamic diagnoses of patients experiencing severe prolonged dysuria showed no persistent symptom or finding which could act as a predictor of those likely to experience problems.

Well over 75% of patients described the urodynamic tests as tolerable, with 6.6% (20/300) saying they actually enjoyed it! Only 14 patients said they found the procedure painful and 16.3% thought it was unpleasant.

## Discussion

Urodynamics testing remains a safe investigative procedure with low morbidity and an infection rate of less than 2%. It is acceptable to the majority of patients, although minimal dysuria should be expected in over 60% of patients and they should be warned about this. Severe prolonged dysuria is much more common in male patients, presumably due to the greater degree of urethral trauma, with approximately 15% suffering for 72 h or more.

Dysuria was not associated with an acquired UTI and we agree that it does not justify the use of prophylactic antibiotics (Bergman and McCarthy, 1983; Copcoat *et al.*, 1988).

Alkalinising agents appeared to be no more successful in treating this dysuria than the glucose placebo we used, although potassium citrate was associated with many unpleasant side effects and was considerably less effective than sodium bicarbonate when the 2 treatments were directly compared.

Telling patients that they are likely to experience initial discomfort for the first 24 to 36 h and advising them to drink 2 to 3 times their normal intake of fluid over this period remains our standard management.

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# Night Studies for Primary Diurnal and Nocturnal Enuresis and Preliminary Results of the "Clam" Ileocystoplasty

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Summary—Modified conventional urodynamic apparatus was used to provide overnight monitoring of bladder and rectal pressure. A group of 26 patients with primary diurnal and nocturnal enuresis underwent both daytime rapid fill cystometry and overnight natural fill cystometry. The overnight study was effective in detecting detrusor instability in 10 patients deemed normal on rapid fill cystometry; 6 of these have now undergone clam ileocystoplasty and 5 are dry; 3 are awaiting this procedure. The clam remains very effective in the management of patients with resistant nocturnal and diurnal enuresis if careful selection is adopted. Overnight cystometry has proved to be an invaluable adjunct to the investigation of patients with primary diurnal and nocturnal enuresis previously felt to be urodynamically normal.

Primary nocturnal enuresis affects about 10% of 6-year-olds, 3% of 12-year-olds and 1% of adults. The condition has a tendency for spontaneous resolution of 15% per year. The advice of a urologist is rarely sought until the condition has been present for many years. Invasive investigation is reserved for resistant cases and urodynamic investigations tend to be undertaken on patients under 15 years of age only if they have severe daytime symptoms in addition to nocturnal enuresis, and in older patients only if they have not responded to conservative treatment. A review of the urodynamic findings in 35 patients on this unit with primary nocturnal and diurnal enuresis revealed a high incidence of urodynamic abnormality (81%), the commonest abnormality being detrusor instability (56% of the total). These findings concur with those of previous authors (Borzyskowski and Mundy, 1987).

The management of the teenager and young adult with primary nocturnal and diurnal enuresis with proven instability on conventional urodynamics is well described and although usually resistant to conservative therapy, the condition is almost always cured by the clam procedure (Lewis *et al.*, 1990). However, the management of the much smaller group of young patients with identical symptoms but normal conventional cystometry is considerably less well described. We therefore employed overnight cystometry in such patients and assessed the results of the clam ileocystoplasty in cases where nocturnal instability was detected.

## Patients and Methods

The series comprised 26 patients, 7 males and 19 females (aged 8–36 years) with resistant primary nocturnal and diurnal enuresis. All underwent conventional filling and voiding videocystometry. Overnight cystometry was then performed using modified Lectromed urodynamic equipment which monitored bladder and rectal pressure via separate Druck transducers. The recording was made on a standard chart recorder which was linked to a chart speed controller; this enabled a paper feed of 1 mm/min under resting conditions, while any rise in bladder pressure of 15 cm $H_2O$ or more triggered a conventional urodynamic paper feed speed of 25 mm/min which persisted until the pressure had

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fallen back to resting levels for 40 s. Thus perusal of an excessively lengthy tracing in the morning was avoided. Most patients were studied for 2 successive nights.

The clam ileocystoplasty was employed in the treatment of selected patients with objective evidence of detrusor instability and its efficacy in controlling their enuresis was assessed.

## Results

The urodynamic and overnight cystometry results are summarised in the Table.

**Table** Results of Urodyanamic Studies and Cystometry

| | *Conventional urodynamics* | *Night study* |
|---|---|---|
| Normal | 16 | 10 |
| Unstable | 6 | 16 |
| Reduced compliance | 4 | 0 |
| Total | 26 | 26 |

N.B. Two patients unstable by day had normal night studies.

Detrusor instability was detected in only 6 patients on conventional urodynamics. Surprisingly, 2 of these did not develop unstable contractions at night. The nocturnal contractions tended to be of higher amplitude and were more prolonged than those demonstrated on routine fast fill cystometry. Ten patients who were deemed normal on conventional assessment showed involuntary detrusor contractions at night. This group comprised 9 females and 1 male. The male patient had a partial success with bladder training, but the females remained resistant to conservative therapy and were offered a clam ileocystoplasty. All but 3 have now had the procedure and all are dry by night, but 1 still has diurnal enuresis. One patient, although dry, has to self-catheterise.

## Discussion

The seemingly low incidence of urodynamic abnormalities (39%) on conventional assessment in this study is due to the selection for overnight cystometry of patients predominantly with normal daytime urodynamics in the hope of detecting evidence of detrusor abnormality not elicited by conventional assessment. Overnight cystometry was undoubtedly successful in this regard. The increased amplitude and prolongation of the unstable contractions compared to rapid fill cystometry is in keeping with our own natural fill ambulatory urodynamic studies and those of others (Webb *et al.*, 1990).

The technique employed in this series for night studies involves a fluid filled system and is therefore unsuitable for ambulatory monitoring but acceptable for supine and sleep monitoring. Allowing natural filling and attempting to allow "normal" sleep is in theory at least more physiological than previous studies using filling cystometry on enuretic children at night (Norgaard, 1989).

Overnight cystometry is a well tolerated, minimally invasive investigation, most appropriately offered to patients with severe nocturnal symptoms who have normal conventional urodynamics. Normal daytime urodynamics in patients who have evidence of detrusor instability detected by overnight cystometry should not preclude the use of the clam ileocystoplasty in their management. The clam remains extremely successful in the management of the older patient with resistant enuresis with proven detrusor instability.

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# Can Histological Assessment Predict the Outcome in Interstitial Cystitis?

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Summary—In a retrospective study we compared the outcome of 39 patients with interstitial cystitis to the histological findings at initial diagnostic bladder biopsy. The degree of inflammation and fibrosis and the mast cell counts were assessed on each biopsy. The prognostic relevance of the clinical features of age, duration of symptoms, frequency, nocturia, pain and bladder capacity was assessed.

The study showed no statistical correlation between the severity of histological findings at diagnosis and the eventual outcome of the disease. Over 50% of patients with severe histological abnormalities responded to conservative treatment. Although the majority of patients with mild pathological changes responded to conservative treatment, some did require surgical intervention.

The clinical features of pain, nocturia and bladder capacity showed significant differences between the 2 patient groups. However, the former 2 features are subject to many variables and the latter probably has too wide a range to be useful as a prognostic indicator.

Only the response of patients to conservative treatment will indicate those who are not being helped and who may eventually require surgical treatment.

Efforts have long been made to characterise the histological appearance of interstitial cystitis (IC) (Hunner, 1914; Messing and Stamey, 1978; Larsen *et al.*, 1982; Fall *et al.*, 1985; Holm Bentzen *et al.*, 1987; Lynes *et al.*, 1987). Hunner (1914) described replacement of the bladder epithelium by chronic granulation tissue, with infiltration by chronic inflammatory cells and fibrosis; he also reported increased numbers of capillaries in the lamina propria, with inflammation only appearing focally in the detrusor layer.

It is generally accepted, as the name implies, that IC is associated with a varying degree of bladder inflammation (Messing and Stamey, 1978; Fall *et al.*, 1985). Much of the recent discussion on this disease, however, has focused on the assessment of mast cell numbers in the bladder wall. A study by Larsen *et al.* (1982) found a highly significant increase in detrusor mast cells in patients with IC and similar results were reported by other authors (Fall *et al.*, 1987; Feltis *et al.*, 1987; Lynes *et al.*, 1987). Despite these findings, 2 reports questioned the specificity of histological findings in IC. One study found a large overlap in terms of symptomatology and cystometric findings in 2 groups of patients with detrusor mast cell counts either greater or less than 28/mm$^2$ (Holm Bentzen *et al.*, 1987). A further study found that, of 65 IC patients who underwent repeat bladder biopsy, only 26 had the diagnosis confirmed on the repeat evaluation (Holm Bentzen, 1988). Hanno *et al.* (1990) also reported no difference in detrusor mast cell counts between 55 IC patients and 21 controls.

We have assessed the histological findings at initial bladder biopsy and attempted to correlate these with the progress of the disease and eventual outcome in that patient. We also studied the correlation between various clinical features and outcome.

## Patients and Methods

The diagnosis of interstitial cystitis was established

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in 39 female patients. This diagnosis was reached on the basis of the National Institutes of Health guidelines (Gillenwater and Wein, 1988). No patient was found to have classical Hunner's ulcers.

Patients were divided into 2 groups according to their response to treatment. Of the 39 patients, 10 (Group A) required radical surgery for treatment of continuing severe symptoms (particularly pain) despite exhaustive conservative treatment. The remaining 29 patients (Group B) were adequately controlled on conservative treatment. This treatment consisted of hydrodistension, dimethyl sulphoxide (DMSO) bladder instillation and sodium pentosanpolysulphate; oxybutynin and phenazopyridine were used empirically as required.

Inflammation, fibrosis and mast cell counts were assessed in bladder biopsies taken at initial cystoscopy for diagnosis. Inflammation was evaluated by assessing the density of inflammatory cells in the various layers following routine haematoxylin and eosin staining. The density and extent of fibrosis was assessed following trichrome staining. Both of these features were scored on a scale of 0 to 4 in order of ascending severity. Mast cell counts were performed, following either Giemsa or toluidine blue staining, using an Olympus BH microscope with drawing-tube attachment at a magnification of 400. The count was performed using a Kurta digitising pad with wireless mouse (Kurta, Phoenix, USA) and an IBM-AT with keyboard and 40 Mbyte hard disk and the Sigma scan image analysis program (Jandel Scientific, Sausalito, USA). This system gives immediate measurement of the area mapped out on a particular tissue section and the mast cell count/mm$^2$ was calculated on this basis. Counts were performed on 10 fields of muscularis in each specimen.

To detect clinical features which might be useful in predicting the course of the disease, the age at diagnosis, duration of symptoms, bladder capacity and degree of urinary frequency, nocturia and pain were assessed.

Statistical analysis was performed using Student's *t* test and Fisher's exact test.

## Results

Initial bladder biopsies were available for review in all but 2 of the 39 patients; 1 of these had already had a cystoplasty prior to referral and the other was referred for surgery after a long history of failure to respond to conservative treatment.

Severe fibrosis in the lamina propria, as defined by a score of 3 or 4, was seen in 4 patients, 2 from Group A and 2 from Group B. The remaining 33 patients with milder fibrosis included 6 in Group A and 27 in Group B (Table 1A). There was insufficient muscle in 8 of 37 trichrome-stained sections to assess fibrosis in this layer. Of the 29 sections assessed, a marked fibrotic reaction was seen in 6, 2 from Group A and 4 from Group B. Mild fibrosis, seen in 23 specimens, occurred in 5 Group A and 18 Group B patients (Table IB). Neither of these results showed a significant difference between the 2 groups ($P=0.56$ for lamina propria fibrosis and $P=0.61$ for muscle). The sensitivity, however, for mild fibrotic change in detecting patients amenable to conservative therapy was 93% and 82% in the respective layers of the bladder wall. The specificity of this finding was somewhat lower, at 82 and 78% respectively.

Inflammation was seen only in the lamina propria in the sections examined. Severe inflammation (score 3–4) was seen in 8 patients, who were distributed equally between the 2 groups. On the other hand, only 4 of the 29 patients with mild inflammatory changes (score of 0–2) were in Group A and 25 were in Group B (Table 1C). Again, differentiation by inflammatory change did not reach statistical significance ($P=0.16$) and both sensitivity and specificity of mild inflammation in detecting a good prognosis amounted to 86%.

Detrusor mast cell counts were available in 28 patients. Mast cell counts $\geqslant 30/\text{mm}^2$ were found in 10 patients, 3 from Group A and 7 from Group B.

**Table 1** A, B and C: Histological Assessment of Findings on Initial Bladder Biopsies—Fibrosis and Inflammation. D: Detrusor Mast Cell Count

| *A. Fibrosis (lamina propria)* | | | *B. Fibrosis (muscle)* | | |
|---|---|---|---|---|---|
| | *Group†* | | | *Group†* | |
| *Score** | *A* | *B* | *Score** | *A* | *B* |
| 3–4 | 2 | 2 | 3–4 | 2 | 4 |
| 0–2 | 6 | 27 | 0–2 | 5 | 18 |
| *C. Inflammation* | | | *D. Mast cell count* | | |
| | *Group†* | | | *Group†* | |
| *Score** | *A* | *B* | *Cells/m*$^2$ | *A* | *B* |
| 3–4 | 4 | 4 | ≥30 | 3 | 7 |
| 0–2 | 4 | 25 | <30 | 3 | 15 |

*Score 0–2: mild or moderate; 3–4: severe.

†Group A: patients requiring surgical intervention. Group B: patients controlled on conservative treatment.

Lower counts were found in 3 patients from Group A and 15 from Group B (Table 1D). Statistical significance was not reached on the basis of mast cell counts ($P=0.31$) and this was not a sensitive method of predicting disease; sensitivity and specificity for detecting mild disease in patients with low mast cell counts were 68 and 83% respectively.

These results indicate that the finding of marked histological changes on initial bladder biopsy in this disease does not necessarily indicate a poor prognosis; indeed, over 50% of these patients were found to be responsive to conservative treatment. It does appear, however, that mild histological abnormalities are reliable predictors of a more benign disease course. Although this did not reach a statistically significant level in the numbers available, of all histological parameters assessed, lack of severe fibrosis in the lamina propria appeared to be the most sensitive in predicting a benign course for the disease.

On examining the 10 bladder specimens removed at the time of substitution cystoplasty, 3 patients were found to have severe fibrosis of the lamina propria; 9 had severe muscle fibrosis, 5 had severe inflammation and 9 had mast cell counts $>30/\text{mm}^2$; however, only 6 of these had initial biopsies available for comparison. Of these factors, only detrusor fibrosis revealed a different pattern when compared with earlier specimens from the same patient, having worsened in 5 patients.

Neither age at presentation, duration of symptoms nor urinary frequency showed a significant difference in predicting the course of the disease (Table 2). However, there was a statistical difference in the degree of nocturia and in the subjective pain score between the 2 groups ($P=0.04$ and $P=0.003$ respectively). There is an obvious difficulty in using subjective pain scores to measure severity of disease, since there is no doubt that such assessment is open to many variables and complicating factors. Although both groups showed a wide range of bladder capacity under general anaesthesia, there remained a statistically significant difference ($P=0.03$) between them.

## Discussion

It is clear that prediction of the course of IC in an individual patient is difficult. The severity of the features used to reach the diagnosis do not necessarily correlate with the prognosis.

The histological abnormalities of bladder inflammation, fibrosis and mastocytosis have been linked with the diagnosis of IC in varying degree for many years. Of the patients in this series who had marked degrees of these features, over 50% responded to conservative treatment. It was also apparent that patients without severe histological disease tended to respond to conservative treatment.

Neither age at presentation nor duration of symptoms predicted the likely outcome of the disease. This latter feature would appear to indicate that the disease is not relentlessly progressive, having reached its maximum severity within a similar time scale in the 2 groups compared. It should be noted, however, that detrusor fibrosis did show an increase at the time of cystoplasty, compared with that noted at initial diagnostic biopsy, in patients who required this treatment. This indicates that severe fibrosis is a progressive change, at least in those patients requiring surgery, and that it will reach this stage relatively early in the course of the disease.

Bladder capacity showed a large variation, even in those patients who required surgery, and a small contracted bladder is not necessarily a feature of the severe disease which causes crippling bladder symptoms and requires surgical correction. Bladder capacity under anaesthesia was, however, the only

**Table 2** Clinical Findings

| | *Group A* | | | | *Group B* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No.* | *Mean* | *Standard deviation* | *Range* | *No.* | *Mean* | *Standard deviation* | *Range* | *P* |
| Age at presentation (years) | 10 | 42.2 | ±14.8 | 20–70 | 29 | 41.4 | ±15.4 | 20–75 | N.S. |
| Duration of symptoms at presentation (years) | 10 | 5.0 | ±5.8 | 1–20 | 29 | 2.7 | ±2.2 | 1–8 | N.S. |
| Frequency (min) | 7 | 31.0 | ±15.0 | 15–60 | 24 | 57.7 | ±39.0 | 15–150 | N.S. |
| Nocturia (times) | 9 | 7.8 | ±5.4 | 3–17 | 28 | 4.9 | ±2.9 | 3–10 | 0.0426 |
| Pain (score 0–4) | 8 | 2.5 | ±0.8 | 2–4 | 29 | 1.6 | ±0.7 | 0–3 | 0.0029 |
| Bladder capacity under G.A. (ml) | 9 | 463.9 | ±243.4 | 150–850 | 28 | 646.1 | ±208.0 | 240-1L | 0.0346 |

truly objective finding which showed a significant difference between the 2 groups. It is probably not possible, however, to use this measure as a very reliable predictor in the individual patient.

Again, although the symptomatic features of pain and nocturia showed a significant difference between the 2 groups, both of these features were subject to many variables and outside influences and are therefore not highly reliable prognostic indicators. This intergroup differentiation is probably due to the fact that continuing severe pain is in itself one of the main indications for surgical intervention in IC.

In summary, the finding of severe histological changes on bladder biopsy in IC does not necessarily predict a poor outcome for the patient. Indeed, over half of such patients are amenable to the conservative treatments available. Similarly, although the majority of patients with mild histological changes do respond well, a small group do not, and require surgical treatment. The differential findings between the 2 groups in pain, nocturia and bladder capacity are not sufficiently specific in the individual patient to be used as predictors of outcome. Only the response, or lack thereof, to conservative treatment will show those patients whose disease is not being controlled and who may, eventually, require surgery. This radical step should be reserved for those patients, about 10% in usual urological practice (Webster and Galloway, 1987), who can no longer maintain a reasonable lifestyle with their bladder *in situ*.

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# Is Voided Urine Suitable for Flow Cytometric DNA Analysis?

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Summary—Samples of bladder washings are frequently used to provide cellular material for flow cytometric DNA analysis. Since voided urine is a potential source of similar material, the aim of this study was to determine whether voided urine yields satisfactory specimens.

We compared the qualitative results of flow cytometric DNA analysis of the cells in 53 specimens of voided urine and 109 samples of bladder washings; 45% (24/53) of urine specimens gave satisfactory DNA histograms compared with 93% (101/109) of bladder washings. This difference was apparent regardless of whether the bladder contained a tumour.

It was concluded that bladder washings provide superior material for flow cytometric DNA analysis and that flow cytometric DNA analysis of freshly voided urine may have deficiencies which preclude its use in routine clinical practice.

Analysis of deoxyribonucleic acid (DNA) using flow cytometry has increasingly been used in the detection and long-term follow-up of bladder carcinoma and can be performed successfully using material from paraffin-embedded tumours, fresh tumour biopsies and bladder washings. Flow cytometric DNA analysis of cells in bladder washings is of value because it is extremely sensitive in the diagnosis and follow-up of patients with bladder cancer (Devonec *et al.*, 1982; Hermansen *et al.*, 1989) and because the results are representative of the DNA content of existing tumours (Chin *et al.*, 1985). In addition, cells in bladder washings are already in suspension and the entire urothelium of the bladder is sampled. However, the collection of bladder washings entails catheterisation or cystoscopy. If voided urine contained suitable cells for flow cytometric DNA analysis and produced results similar to those of bladder washings, the need for catheterisation would be obviated. There would also be enormous potential for the technique to be adopted as a screening procedure for high risk groups of patients and as a non-invasive method of monitoring patients with a history of bladder cancer, potentially reducing the frequency of cystoscopic examinations.

## Patients and Methods

An analysis was made of 109 samples of bladder washings and 53 specimens of freshly voided urine (including 28 paired samples) collected from 134 urological patients. The urological diagnoses are listed in Table 1.

**Table 1** Urological Procedures in Patients Providing Samples

| *Urological procedure* | *Voided urine* | *Bladder washings* |
|---|---|---|
| Bladder tumour resection | 27 | 55 |
| Check cystoscopy | 3 | 13 |
| Cystoscopy (benign disease) | 13 | 24 |
| TURP | 6 | 14 |
| Others | 4 | 3 |
| Total | 53 | 109 |

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

Samples of voided urine, other than the first void of the day, were collected pre-operatively and bladder washings were obtained at the time of initial cystoscopy using an Ellik evacuator filled with normal saline. Urine samples were either analysed immediately or stored at 4°C. If there was a delay of more than 6 h before analysis, the cells were transferred to phosphate buffered saline (PBS). Bladder washings were refrigerated as collected prior to analysis. More than 80% of samples were analysed within 24 h and the remainder were tested within 48 h.

Following centrifugation at 2500 rpm for 10 min, the supernatant was decanted and the cell pellet resuspended in PBS. The resuspended pellet was passed through a 30 micron filter to remove large debris and clumps of cells. Samples were stained according to the method of Taylor (1980) with propidium iodide (PI; 50 µg/ml), Triton X-100 (1%) and RNAase (1 mg/ml) and analysed on a flow cytometer (FACSCAN—Becton-Dickinson) which was preset to collect 10,000 cells. Excitation of the PI fluorochrome was performed by a 488 nm 15 mWatt argon laser. Fluorochrome emission at 630 nm was measured on a photomultiplier tube with laser light filtration, first with a 640 nm dichroic mirror and then with a 585 ± 42 band pass filter (Fluorescence 2). Linear amplification was used on forward scatter, side scatter and Fluorescence 2 parameters. During the course of sample analysis the rate of cell data acquisition was adjusted to less than 500 cells/s by diluting the sample with the Triton/PI staining solution. To remove non-stained debris a gate of 12-255 was used on the Fluorescence 2 parameter and a low threshold on forward scatter was used to exclude debris. Normal peripheral blood lymphocytes were used as an external control to indicate diploid amounts of DNA.

Data were collected using the Consort 30 software package (Becton-Dickinson) and the results of nuclear stain expressed as histograms. Histograms had to fulfil the following 3 criteria to be classified as satisfactory for subsequent determination of ploidy:

(1) Sufficient cells in the sample for analysis (>10,000).
(2) Coefficient of variation (CV) of the main peak <10%.
(3) Particles to the left of the diploid peak accounting for <50% of the 10,000 events.

These criteria were selected because they defined the limits of a histogram with accurate, interpretable peaks on the Fluorescence 2 PI detector.

## Results

Combining the paired and unpaired data, 45% (24/53) of urine specimens gave satisfactory DNA histograms compared with 93% (101/109) of bladder washings ($\chi^2 = 42.77$ with 1 DF; $P < 0.001$). This difference was apparent regardless of whether the patient had a bladder tumour or a benign urological disorder: 48% (13/27) of voided urines and 93% (51/55) of bladder washings from patients with bladder tumours gave satisfactory histograms and 42% (11/26) of urine specimens and 93% (50/54) of bladder washings from patients with benign disorders gave satisfactory results.

The results from the 28 paired samples are of most interest. The histogram characteristics are shown in Table 2. In 8 urine samples the DNA histogram profiles were so poor that even measurement of the CV and the amount of debris was not possible. Of the remaining 20 urine samples, it can be seen that their CVs were larger and more debris was present compared with the 28 bladder washings. Only 7 voided urine samples (25%) resulted in satisfactory histograms compared with 24 bladder washings (86%) ($P < 0.001$). The reasons for disqualifying 21 urine samples and 4 bladder washings are shown in Table 3.

**Table 2** Histogram Characteristics

| | | *CV (%)* | | *% Debris* | |
|---|---|---|---|---|---|
| | *No.* | *Mean* | *Range* | *Mean* | *Range* |
| Urine | 20* | 9.5† | 4.4–16.0 | 40.6‡ | 9.7–80.3 |
| Bladder washings | 28 | 7.3† | 3.3–15.9 | 15.6‡ | 1.9–45.6 |

* The quality of histograms from 8 urine samples did not permit measurement of CV and % debris.
† $P < 0.014$.
‡ $P < 0.0001$.

**Table 3** Reasons for Disqualifying Histograms

| | *No.* | *CV > 10%* | *Debris > 50%* | *Insufficient cells* |
|---|---|---|---|---|
| Urine | 21/28 | 8 | 13 | 4 |
| Bladder washings | 4/28 | 3 | 0 | 1 |

2 urines had CV > 10% plus debris > 50%.
2 urines had debris > 50% plus insufficient cells.

In 17/28 patients (61%) a satisfactory histogram was obtained from bladder washings but the histogram from voided urine was unsatisfactory (Fig. 1). The converse result was not observed. In the 7 patients in whom the histograms from urine were satisfactory, 3 specimens gave results similar to those of the bladder washings (Fig. 2), but 4 gave dissimilar results (Fig. 3).

The correlation of histogram results with clinical findings was not the purpose of this study, but interesting findings were observed. Patient 7 had abnormal DNA histograms from both urine and

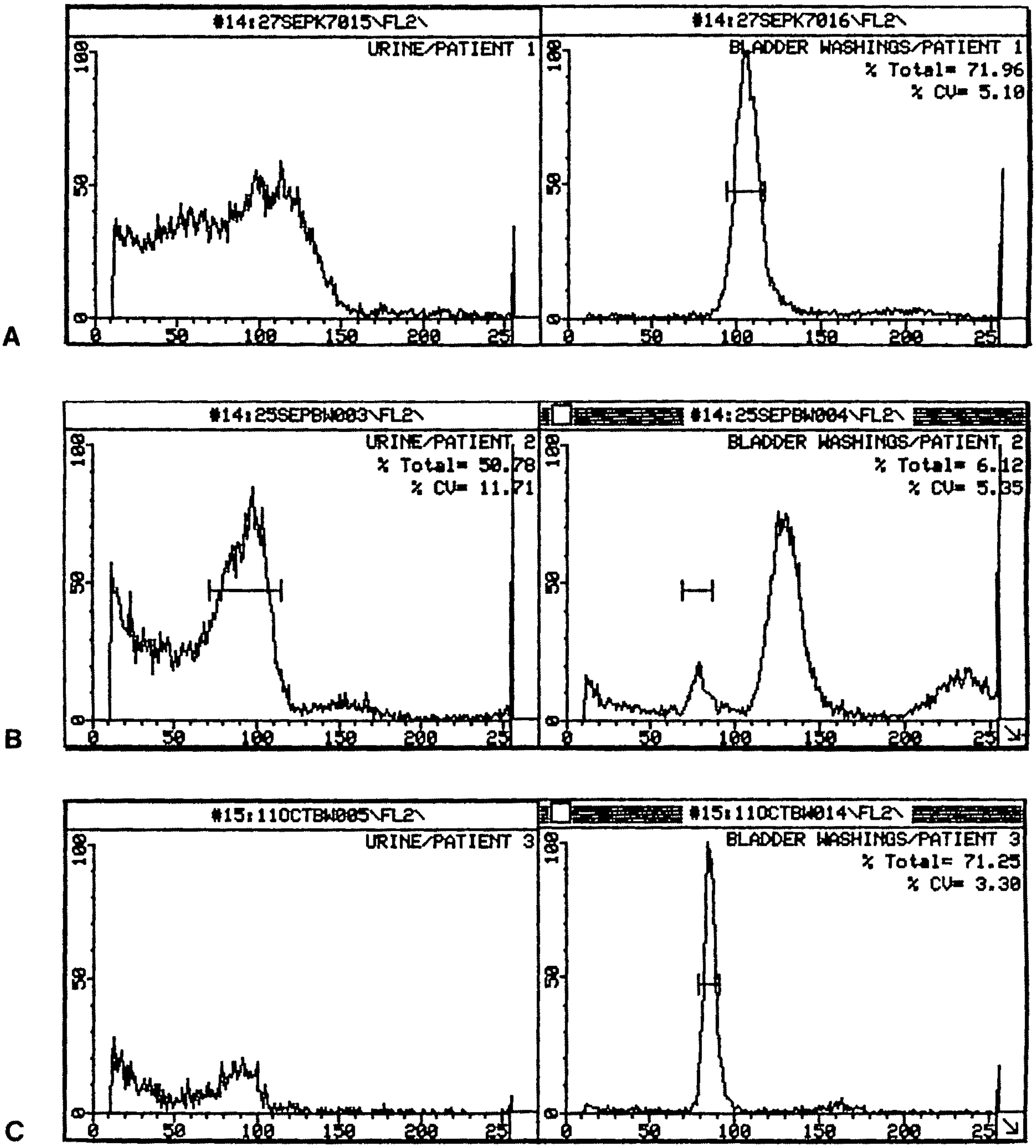

**Fig. 1** Satisfactory DNA histograms from bladder washings and unsatisfactory histograms from voided urine. Urine samples unsatisfactory because of excessive debris. (A), broad peak with large CV (B) and insufficient cells (C).

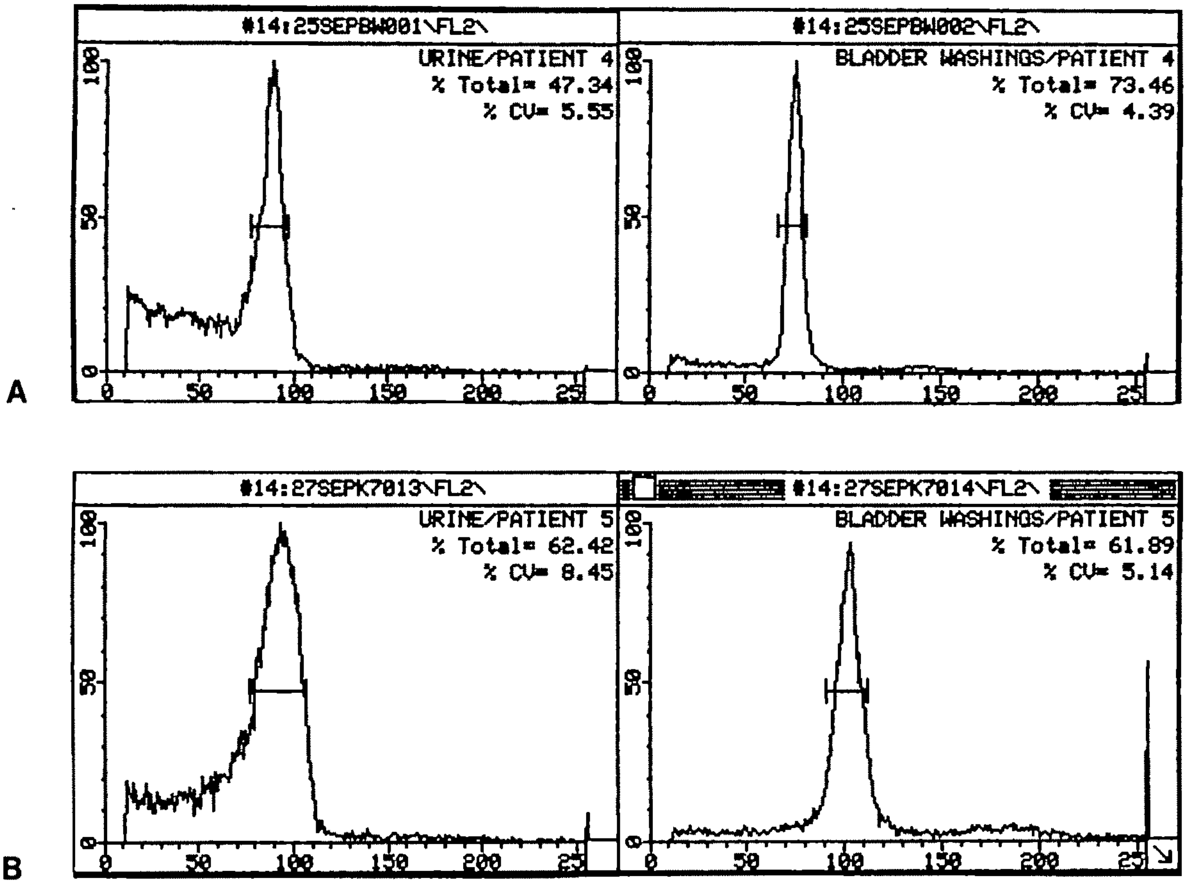

**Fig. 2** Examples of similar DNA histograms obtained from bladder washings and urine.

bladder washings (Fig. 3A) and at the time of initial cystoscopy had a macroscopically normal bladder. However, at a subsequent cystoscopy she was found to have carcinoma *in situ* of the bladder. Flow cytometric abnormalities predating cystoscopic abnormalities have been widely reported. Patient 8 had a T1 G3 bladder tumour with concomitant carcinoma *in situ* and although the DNA histogram from bladder washings indicated the presence of abnormal cells, the histogram from urine appeared normal (Fig. 3b).

## Discussion

Whilst the diagnostic and prognostic value of DNA analysis by flow cytometry has been demonstrated using cells from bladder washings, the value of nuclear analysis of cells in voided urine remains controversial. Our results suggest that voided urine does not provide satisfactory material for flow cytometric analysis compared with bladder washings.

In a similar study, Konchuba *et al.* (1989) found that specimens which were fixed in 25% ethanol soon after collection were superior to unfixed samples. However, in agreement with our results, they reported that bladder washings provided a greater proportion of satisfactory DNA histograms (67% unfixed, 90% fixed) compared with voided urine (41% unfixed, 66% fixed). These authors stressed the need to fix cells within 60 min of collection to prevent rapid deterioration, although in our experience cooling of bladder washings to 4°C also provided satisfactory histograms with the potential advantage of staining with monoclonal antibodies against cell surface antigens.

Other authors have reported satisfactory results using voided urine. In 1985, Pritchett *et al.* reported a successful method of analysis of voided urine in 5 patients with benign urothelial disorders and 7

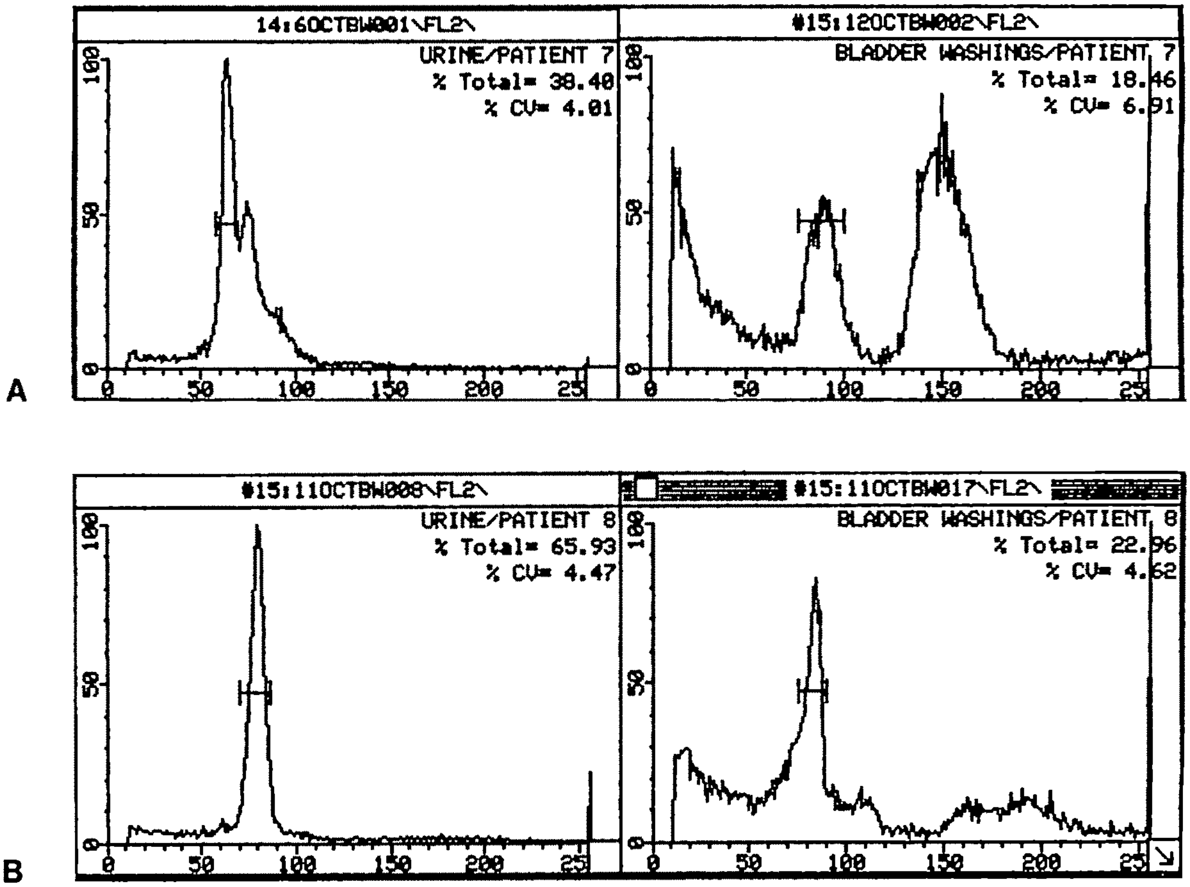

Fig. 3 Examples of dissimilar DNA histograms obtained from bladder washings and urine.

patients with transitional cell carcinoma of the bladder. However, only selected groups were studied: the non-malignant patients were deliberately chosen on the basis that they had hypercellular urine and most of the patients with bladder cancer had high grade, high stage tumours or carcinoma *in situ*. These investigators concluded that 90% of urine samples proved adequate when compared with bladder washings, but it is not clear if their judgement was based on the results from this small study or on a larger series of unpublished results.

More recently, DeVere White *et al.* (1988) analysed 114 samples of bladder washings and 122 urine specimens from 89 patients with either a previous history of transitional cell carcinoma of the bladder or active disease. It should be pointed out that only 29 specimens were true voided urine samples; 53 samples were taken on catheterisation and 40 were obtained at cystoscopy. Overall, only 3/114 bladder washings (2.6%) and 5/122 urine samples (4%) [1 (3.4%) voided urine sample] were unsatisfactory. Although unsatisfactory samples were stated as having low cell numbers, excessive debris or unresolvable peaks, precise definitions of criteria for satisfactory histograms were not described. This group obtained good results despite allowing samples to remain at room temperature for up to 6 h (*vide supra*) and reported that in 26 cases (23%), urine samples actually resulted in superior histograms compared with bladder washings. Presumably, differences in methodology or differences in the definition of a satisfactory histogram account for the discrepancies in the results from different centres.

Bladder washings usually provide better material than voided urine for routine conventional cytological examination (El-Bolkainy, 1980) because of greater numbers of cells, better cell preservation and fewer contaminants (inflammatory cells, squamous cells, red blood cells, urinary crystals, cellular debris, bacteria and sperms). It is, therefore, not entirely unexpected to find that bladder washings provide superior material for flow cytometric analysis. However, it may be that in the future, more sensitive flow cytometric techniques will be able to compensate for the deficiencies in voided urine samples.

Our results argue strongly against the feasibility of flow cytometric DNA analysis of cells in voided urine using relatively straightforward methods. Several groups have reported improved results using urine following fixation of samples (Konchuba *et al.*, 1989; Deitch *et al.*, 1990), although this may adversely affect the analysis of other important cellular antigens. Other modifications of technique to improve results include the use of density gradients to enrich the urothelial cell population, the use of tissue specific markers such as cytokeratins (Feitz *et al.*, 1985) or T16 antigen (Bretton *et al.*, 1989) and the electronic gating of cells.

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# Clinical Significance of the "Palpable Mass" in Patients with Muscle-infiltrating Bladder Cancer Undergoing Cystectomy after Pre-operative Radiotherapy

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Summary—Between 1976 and 1985, 132 patients with T2/T3/T4a bladder cancer underwent cystectomy after pre-operative radiotherapy (46 Gy: 67 patients; 20 Gy: 65 patients). After a median time of 41 months, 62 patients were alive; 51 had died from recurrent bladder cancer and 19 from intercurrent disease without recurrence of their malignancy. Distant metastases developed in 40 patients, accompanied in 5 cases by local recurrence. Local recurrence was the first sign of relapse in 11 patients. In 3 patients the localisation of the relapse remained unknown.

The corrected 5-year survival rate was 60%. T category and a palpable bladder tumour were independent pre-treatment prognostic factors in a Cox regression analysis, together with the interval between initial diagnosis and cystectomy. The presence of a palpable tumour before the start of treatment was associated with a particularly poor prognosis in T3/T4a tumours, whereas the survival of patients with non-palpable T3/T4a tumours was similar to that of patients with T2 bladder cancer. Another important prognostic factor was post-irradiation stage reduction (no residual muscle infiltration in the cystectomy specimen). Significantly more patients with non-palpable bladder tumours experienced post-radiation stage reduction than did those with a palpable tumour. However, the prognostic value of stage reduction was statistically significant only in patients with palpable bladder tumours.

Total cystectomy and high dose radiotherapy are the 2 treatments used in an attempt to cure patients with muscle-infiltrating bladder cancer (Bloom *et al.*, 1982; Werf-Messing *et al.*, 1982; Jacobi *et al.*, 1983; Hope-Stone *et al.*, 1984; Montie *et al.*, 1984; Whitmore and Batata, 1984; Fosså *et al.*, 1985; Marcial *et al.*, 1985; Shipley *et al.*, 1985; Quilty *et al.*, 1986), but the 5-year survival rates rarely exceed 50%. In the hope of improving these results, total cystectomy is occasionally combined with preoperative pelvic radiotherapy, although the value of this treatment has not been fully established (Bloom *et al.*, 1982; Werf-Messing *et al.*, 1982; Anderstrøm *et al.*, 1983; Whitmore and Batata, 1984; Fosså *et al.*, 1986).

During the early 1970s, high dose radiotherapy was the treatment of choice for patients with muscle-infiltrating bladder cancer in Norway. Since 1975, total cystectomy has increased in popularity. In 1986 we presented our short-term observations on 122 patients with T2/T3/T4a bladder cancer undergoing cystectomy, either with or without preoperative radiotherapy (Fosså *et al.*, 1986). We now present the long-term results in 132 patients with T2/T3/T4a bladder cancer treated by cystectomy after preoperative radiotherapy between 1976 and 1985. An attempt is made to define the prognostic factors which are relevant in a multicentre study.

## Patients and Methods

The series comprised 132 patients with histologically proven, muscle-infiltrating bladder carcin-

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oma: between 1976 and 1985 they underwent radiotherapy prior to cystectomy at the Norwegian Radium Hospital (NRH). Radiotherapy was given according to the urologist's preference. Patients who underwent surgery at the NRH received 2 Gy × 23 over 4½ weeks (Subgroup 1). Those who were treated at other hospitals received 4 Gy × 5 over one week (Subgroup 2). All patients were treated daily (5 times per week) and treatment was applied to both anterior and posterior fields, covering the pelvic structures up to the sacral promontory. Cystectomy was carried out 3 to 4 weeks later in patients treated at the NRH, whereas those receiving 20 Gy underwent operation during the week following radiotherapy.

Further information on the patients is given in Table 1. The period between initial diagnosis of bladder carcinoma and cystectomy was defined as the post-diagnostic interval. T category was assessed before radiotherapy, according to UICC criteria 1978/1982, based on the results of cystoscopy, transurethral resection of the bladder tumour (TUR-B) and bimanual palpation (UICC, 1978). The tumour was regarded as T2 (60 patients) if there was no palpable mass after TUR-B and no histological evidence of deep muscle infiltration (see below). Of 72 patients with T3/T4a tumours, 62 had a palpable mass remaining after TUR-B. In the other 10 patients a mass in the bladder wall was not palpable by rectal examination but there was histological evidence of deep muscle infiltration. In these patients the urologist had performed a fractionated TUR-B, separating the superficial muscular layer from its deep portion and storing the histological material in different containers. No attempt was made to discriminate between T3a and T3b categories.

All histological material was reviewed by the NRH Department of Pathology and the following factors were considered: histological grade (UICC, 1978), invasion of small vessels and depth of infiltration in the cystectomy specimen. Post-radiotherapy stage reduction was defined as the absence of muscle infiltration in the cystectomy specimen or the absence of infiltration in the prostate if this had been demonstrated in the pre-treatment biopsy.

**Table 1** Details of patients

| | *Subgroup 1 46 Gy* | *Subgroup 2 20 Gy* | *Total* |
|---|---|---|---|
| No. of patients | 67 | 65 | 132 |
| No. of institutions | 1 | 12 | 13 |
| Males/females | 49/18 | 56/9 | 105/27 |
| Median age (years) | 64 | 66 | 64 |
| Range | (41–81) | (25–75) | (25–81) |
| Post-diagnosis interval (months) | 6<br>(2–227) | 3<br>(0–201) | 5<br>(0–221) |
| T category | | | |
| T2 | 30 | 30 | 60 |
| T3 | 35 | 30 | 65 |
| T4a | 2 | 5 | 7 |
| Palpable mass | | | |
| Present | 34 | 36 | 70 |
| Absent | 33 | 29 | 62 |
| Grade (WHO) | | | |
| 2 | 17 | 16 | 33 |
| 3 | 49 | 46 | 95 |
| Undifferentiated | | 2 | 2 |
| squamous cell carcinoma | 1 | 1 | 2 |
| Small vessel infiltration | | | |
| Present | 35 | 33 | 68 |
| Absent | 32 | 32 | 64 |
| Median observation time (months) | 41 | 41 | 41 |
| Range | (2–138) | (1–100) | (1–138) |

Cystectomy included the peritoneum, seminal vesicles, prostate and the lower ends of the ureters, which were removed *en bloc*. In women the whole urethra, anterior and lateral walls of the vagina, the ureters, fallopian tubes and ovaries were included in the surgical resection. Pelvic lymphadenectomy was recommended but was not mandatory. Most patients underwent at least a limited resection of the lymph nodes in the obturator space as a staging procedure.

All patients were followed up until 31 December 1989, at intervals of 3 to 6 months during the first 3 years and at least once a year thereafter. The median observation time was 41 months. The minimum observation time in surviving patients was 3 years.

At each follow-up the patient underwent a general clinical examination and rectal examination of the pelvis. Chest X-ray and/or specific investigations of the skeletal system or the liver were carried out if there was clinical suspicion of metastases.

## Statistics

Medians and ranges were calculated using the PC-based statistical package "Medlog". Differences between distributions were assessed by the Wilcoxon rank test and the $\chi^2$ test. Unless otherwise stated, the 5-year corrected survival rate was calculated; all patients dying from or with active bladder cancer were considered to be failures. The logrank test was used to evaluate differences between survival rates. In order to evaluate independent prognostic parameters a forward step Cox regression analysis was done. A $P$ value $<0.05$ was regarded as statistically significant.

## Results

At the time of the last observation 60 patients were alive with no evidence of disease; 19 had died from intercurrent disease without recurrence of their bladder cancer and 2 were alive with metastases (Table 2a). Metastases and/or local recurrence developed in 54 patients within 12 months (median) of cystectomy (Table 2b, Fig. 1). In 6 of 37 patients with no residual tumour in the cystectomy specimen (pTO) distant metastases were detected during follow-up.

The corrected 5-year survival rate was 60% for all patients (Fig. 2). The overall crude survival rate (all deaths considered) was 50%.

In the univariate analysis, the only clinical or pathological factor known before treatment which significantly affected the prognosis was the T category: patients with T2 tumours had a 70% 5-year survival rate, whereas 50% of patients with T3/T4a tumours survived for 5 years (Fig. 3). The $P$ value decreased from $P$:0.02 to $P$:0.009 if groups both with and without a palpable mass after TUR-B were compared without regard to the T category (Fig. 4). The reason for the better discriminative ability of the criterion "palpable mass" was the fact that the 10 patients with non-palpable T3/T4a tumours had a survival curve similar to that seen in patients with T2 tumours (Fig. 5). The limited number of patients, however, meant that the survival difference between patients with non-palpable and palpable T4/T4a tumours was not statistically significant.

No relationship was found between the palpability of the bladder tumour and most clinical or histological factors known before treatment. The only exception was the median post-diagnostic interval, which was significantly shorter in patients with a palpable bladder tumour than in those with non-palpable carcinomas (Table 3).

Stage reduction was another statistically significant prognostic factor (Fig. 6) which was greatest for patients with palpable tumours and achieved significance only in this subgroup (Fig. 7). Stage reduction was significantly correlated with the presence of a palpable mass at the start of treatment: 62% of the (non-palpable) T2 tumours underwent stage reduction, whereas this occurred in only 27% of the palpable T3/T4a tumours (Table 4), with non-palpable T3/T4a tumours lying between these 2 values (50%). None of the other histological or clinical pre-treatment variables correlated significantly with stage reduction. In particular, survival was the same for patients receiving 20 Gy as for those treated with 46 Gy.

**Table 2** Clinical Course

| | *Subgroup 1 46 Gy* | *Subgroup 2 20 Gy* | *Total* |
|---|---|---|---|
| (a) *Status at last observation* | | | |
| No. of patients | 67 | 65 | 132 |
| Alive, no evidence of disease | 31 | 29 | 60 |
| Alive with disease | | 2 | 2 |
| Dead from intercurrent disease, no recurrent tumour | 6 | 13 | 19 |
| Dead from/with bladder cancer | 30 | 20 | 51 |
| (b) *Relapse* | | | |
| Distant metastases | 20 | 15 | 35 |
| Local recurrence | 6 | 5 | 11 |
| Distant metastases + local recurrence | 4 | 1 | 5 |
| Unknown localisation | 1 | 2 | 3 |
| Total | 31 | 23 | 54 |
| Median time to relapse (months) | 12 | 14 | 12 |
| Range | (11–68) | (4–61) | (4–68) |

In the Cox regression analysis the post-diagnostic interval (used as continuous variable) was the only additional pre-treatment variable which significantly and independently predicted prognosis if the

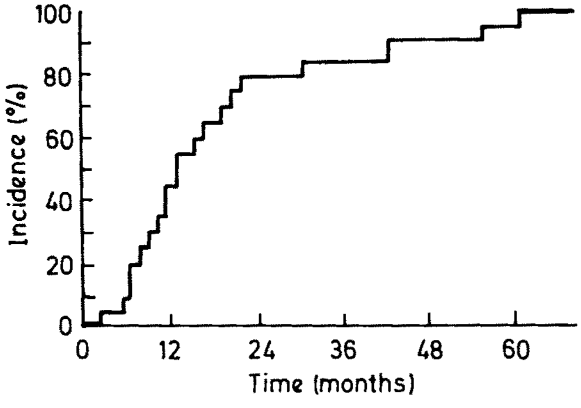

**Fig. 1** Cumulative incidence of local recurrence and/or distant metastases.

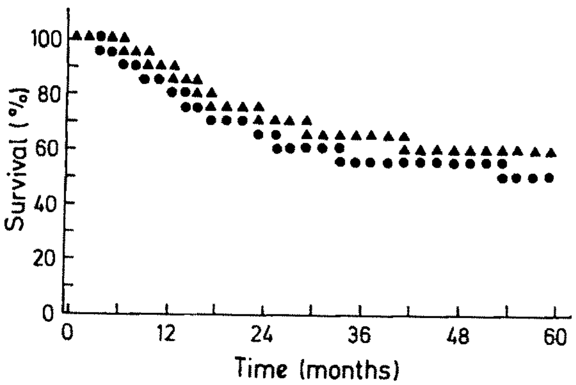

**Fig. 2** Corrected (▲) and crude (●) survival after cystectomy.

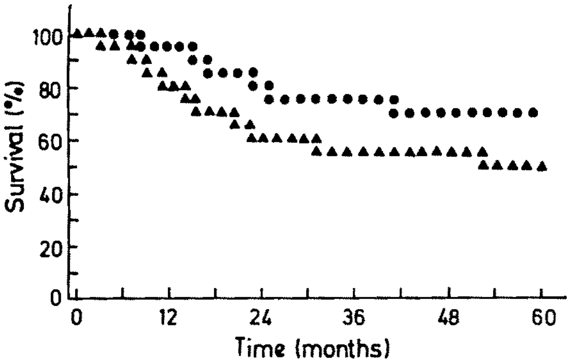

**Fig. 3** T category and corrected survival after cystectomy. P = 0.02. ●● T2 (60 patients); ▲▲ T3/T4a (72 patients).

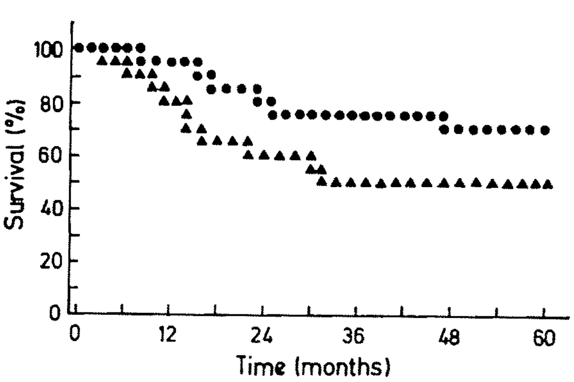

**Fig. 4** Palpable mass and corrected survival. $P=0.009$. ●● No palpable mass (70 patients); ▲▲ Palpable mass (62 patients).

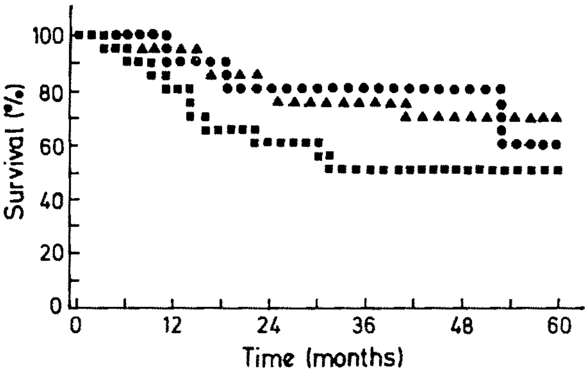

**Fig. 5** T category/palpable mass and corrected survival. T2 No palpable mass (60) ▲▲. T3/T4a ($P=0.3$): No palpable mass (10) ●●; Palpable mass (62) ■■.

palpability of the tumour served as the first prognostic parameter. This was due to the fact that a long diagnostic interval worsened the prognosis for non-palpable tumours (Fig. 8). If palpability of the tumour and stage reduction were considered together, both variables proved to be independent prognostic parameters.

## Discussion

Our corrected 5-year survival rate of 60% is surprisingly high when compared with the results of other cystectomy series (Bloom *et al.*, 1982; Montie *et al.*, 1984; Whitmore and Batata, 1984). This is probably because our patients were highly selected, representing a "good risk group". This is consistent with the fact that, according to figures from the Norwegian Cancer Registry (personal communication, 1989), our series comprised only 10% of patients presenting with muscle-infiltrating bladder cancer in the southern part of Norway, diagnosed between 1976 and 1985.

The high frequency of distant metastases, even in patients with pT0 tumours, remains a matter of concern in the curative management of muscle-infiltrating bladder cancer and confirms the claim by Prout *et al.* (1979) that this malignancy must often be regarded as a "systemic disease". Further clinical research is required to establish whether modern adjuvant chemotherapy can improve the outcome for these patients (McCullough *et al.*, 1989; Raghavan *et al.*, 1988; Scher *et al.*, 1988; Splinter *et al.*, 1988).

The methods used for pre-treatment discrimination between T2 and T3 bladder carcinomas in the routine management of this disease have been discussed by Schröder *et al.* (1988) and Hendry *et*

**Table 3** Palpable Mass and Pre-treatment Clinical/Histological Factors

| | *Palpable mass* | |
|---|---|---|
| | *No* | *Yes* |
| No. of patients | 70 | 62 |
| T2 | 60 | |
| T3/T4a | 10 | 62 |
| Grade | | |
| 2 | 19 | 14 |
| 3 or non-transitional cell carcinoma | 51 | 48 |
| Small vessel infiltration | | |
| Present | 34 | 31 |
| Absent | 36 | 31 |
| Interval following diagnosis (months) | | |
| ≤4 | 36 | 43 |
| >4 | 34 | 19 |
| Median* | 6 | 4 |
| Range | (1–221) | (0–82) |

*$P<0.05$.

*al.* (1990). It is hoped that the latest imaging techniques (computed tomography (CT) and ultrasonography) will prove helpful. However, the interpretation of CT and ultrasonography findings in bladder cancer remains controversial and accurate discrimination does not seem possible by these means (Jaeger *et al.*, 1986; Sager *et al.*, 1983, 1988). Furthermore, neither CT nor ultrasonography is available at all institutions which treat bladder cancer patients. To discriminate between T2 and T3 bladder tumours the 1978/82 TNM classification system (UICC, 1978) recommends clinical examination combined with the results of histological assessment of the TUR-B specimen. In the event of a residual mass remaining after TUR-B and/or histological evidence of deep muscle invasion, the tumour should be categorised as T3. The TNM classification system (UICC, 1987) has omitted the residual palpable mass as a criterion for discrimination between T2 and T3 tumours. T2 tumours are defined as those with superficial muscular infiltration, where T3 tumours infiltrate the deep part of the muscular layer of the bladder wall.

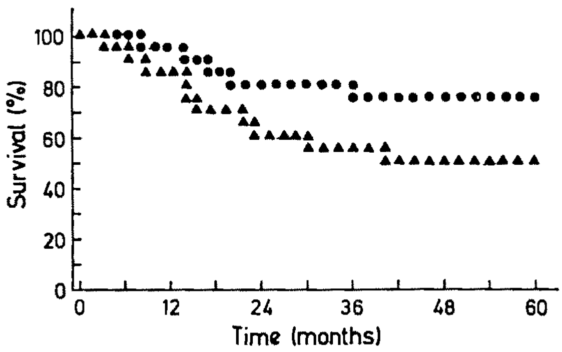

**Fig. 6** Stage reduction and corrected survival. $P=0.005$. ●● Stage reduction (59); ▲▲ No stage reduction (73).

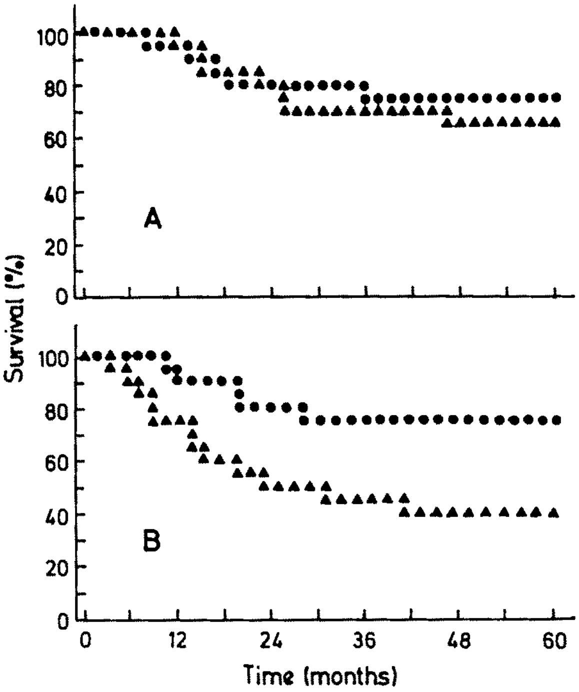

**Fig. 7** Palpable mass/stage reduction and corrected survival. (A) No palpable mass: ●● Stage reduction (42); ▲▲ No stage reduction (28). (B) Palpable mass ($P=0.027$); ●● Stage reduction (17); ▲▲ No stage reduction (45).

The pathologist is usually unable to make a firm diagnosis of deep muscle infiltration in TUR-B material where any orientation of the tissue is lacking. This might occasionally be possible if fractionated TUR-B is performed and the deep muscular layer is sent to the pathology laboratory in a separate container. However, in the routine management of bladder cancer, fractionated TUR-B seems to be a rare event.

The 1987 TNM recommendations for bladder cancer have been discussed by the EORTC GU Group (Schröder *et al.*, 1988) and judged to be a retrograde step because they probably diminish the applicability of the T category as a prognostic parameter. The present study shows that the presence of a palpable mass after TUR-B does help to discriminate between T2 and T3/T4a tumours

**Table 4** Palpable Mass and Post-radiotherapy Stage Reduction

| | *Stage reduction* | | |
|---|---|---|---|
| | *No* | *Yes* | *Total* |
| No. of patients | 73 | 59 | 132 |
| Non-palpable mass | | | |
| T2 | 23 | 37 | 60 |
| T3/T4a | 5 | 5 | 10 |
| Palpable mass | | | |
| T3/T4a | 45 | 17 | 62 |

and may give additional prognostic information within each of these 2 subgroups: the prognosis of patients with non-palpable T3/T4a tumours seems to mirror that of patients with T2 tumours rather than palpable T3/T4a tumours. Furthermore, stage reduction occurs more often in non-palpable tumours, although its prognostic significance is greater in patients with palpable tumours.

The value of pre-cystectomy radiotherapy has been discussed extensively (Miller, 1980; Anderstrøm *et al.*, 1983; Jacobi *et al.*, 1983; Whitmore and Batata, 1984) and many workers now regard it as unnecessary. The present series cannot contribute to this discussion. On the other hand, post-irradiation stage reduction is undoubtedly related to a favourable prognosis, especially in patients with a palpable tumour. This agrees with the observations of Werf-Messing *et al.* (1982) who showed that palpable stage reduction before cystectomy was a significant factor for improved survival in T3 bladder cancer patients. The improved prognosis after radiotherapy may be a result of irradiation-induced tumour reduction. Alternatively, stage reduction may simply indicate the presence of a less aggressive tumour which would have been associated with a good prognosis regardless of radiotherapy. Today, neo-adjuvant chemotherapy is increasingly used in patients with muscle-infiltrating bladder cancer (Scher *et al.*, 1988; McCullough *et al.*, 1989; Splinter *et al.*, 1988). Stage reduction is seen in about 50% of patients and (as with radiotherapy) chemotherapy-induced stage reduction is related to an improved prognosis. Further research is needed to demonstrate the relationship between post-chemotherapy stage reduction, the palpability of the bladder tumour and prognosis.

In conclusion, muscle-infiltrating operable bladder cancer patients can be divided into 2 prognostic groups: those with and those without palpable tumours after TUR-B. Most patients without palpable tumours have T2 tumours. Those with histologically confirmed deep muscle infiltration (T3/T4a), but without a palpable tumour, appear to have a better prognosis than similar patients who have a palpable tumour.

In prospective trials comprising patients with muscle-infiltrating bladder cancer, the palpability of the tumour should always be recorded because it provides significant prognostic information. Further clinical research has yet to show how far more objective investigations (computed tomography, ultrasonography and/or nuclear magnetic resonance) can replace the criterion of a palpable mass and whether they will provide similar (or better) prognostic information.

If pre-cystectomy radiotherapy is given, stage reduction occurs significantly less often in patients with palpable tumours than in those with non-palpable tumours. However, if stage reduction does occur, it is of greater prognostic importance in patients with a palpable tumour than in those whose tumour is not palpable after TUR-B.

The development of distant metastases after cystectomy remains a problem in the treatment of

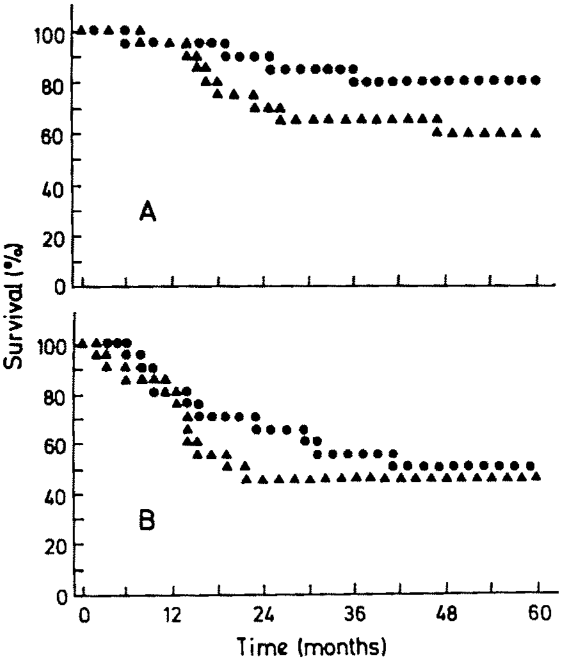

**Fig. 8** Palpable mass/post-diagnostic interval and corrected survival. (A) No palpable tumour ($P = 0.09$); ●● Post-diagnostic interval ≤4 months (36); ▲▲ Post-diagnostic interval >4 months (34). (B) Palpable tumour ($P = 0.36$): ●● Post-diagnostic interval ≤4 months (43); ▲▲ Post-diagnostic interval >4 months (19).

muscle-infiltrating bladder cancer. In this respect, the investigation of adjuvant chemotherapy may prove useful.

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# Radical Radiation Treatment of Invasive and Locally Advanced Bladder Carcinoma in Elderly Patients

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Summary—A total of 146 patients with invasive or locally advanced carcinoma of the bladder (T2–T4) underwent radiation treatment. A significantly higher complete response rate was observed with doses equal to or above 55 Gy and with doses corresponding to cumulative radiation effect (CRE) values of 1700 radiation effect units (reu) or more. In multivariate analysis, decreasing time from the first diagnosis of bladder carcinoma to radiation treatment and 1 or more transurethral resections was associated with a significant increase in survival; increases in T category and sedimentation rate were negative prognostic factors. Although both radiation dose and CRE levels had a significant effect on survival in univariate analysis, an increase in CRE levels alone was associated with a significant increase in survival in multivariate analysis. However, the most important predictor of survival was whether the patient showed a complete local response or not. This study emphasises the importance of treating patients with an adequate radiation dose over a short period of time in order to achieve the maximum radiobiological effect and thereby increase the possibility of cure.

The management of muscle-infiltrating tumours (T2–T3 according to the UICC (1978) TNM classification) and tumours extending beyond the bladder wall (T4) has long been controversial (Prout *et al.*, 1973; Wallace and Bloom, 1976; Herr *et al.*, 1983; Whitmore, 1983). Pre-operative radiotherapy combined with cystectomy ± chemotherapy is generally considered the best treatment with regard to local control and survival (Wallace and Bloom, 1976; Herr *et al.*, 1983; Whitmore, 1983). A 5-year survival rate of 33 to 50% in patients with T3 tumours has been reported (Prout *et al.*, 1973; Werf-Messing, 1975; Wallace and Bloom, 1976; Whitmore *et al.*, 1977; Jakse *et al.*, 1985). However, about 40% of patients with T2–T4 tumours develop metastatic disease (Whitmore *et al.*, 1977; Jakse *et al.*, 1985; Marks *et al.*, 1988) and local recurrence is noted in approximately 20% (Whitmore, 1983; Jakse *et al.*, 1985; Marks *et al.*, 1988). When considering the cancer-related death rate, morbidity of urinary diversion, loss of sexual function and surgically related mortality rate of 1 to 8% (Wallace and Bloom, 1976; Jakse *et al.*, 1985; Wood *et al.*, 1987), these results are not satisfactory. In elderly patients with an increased risk of treatment-related complications and morbidity, an alternative treatment is radical radiotherapy, which has fewer side effects but a lower 5-year survival rate of 10 to 35% in locally advanced tumours (Werf-Messing, 1965, 1975; Goffinet *et al.*, 1975; Fisch and Fayos, 1976; Wallace and Bloom, 1976; Bloom, 1978; Hope-Stone *et al.*, 1981). Thus a higher degree of tumour eradication with organ conservation is a major goal in the treatment of infiltrating and locally advanced tumours in these patients.

The aim of this study was to identify prognostic factors present at the start of radiotherapy. In addition, the effect of radiation on local tumour regression and survival was studied, and the extent to which local tumour regression could predict survival.

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## Patients and Methods

### *Patients*

Between June 1976 and November 1981 (65 months), 155 patients (43 females, 112 males) with T2–T4 bladder carcinoma and no history of other malignancy were referred to the Department of Oncology, Haukeland Hospital. Nine patients received pre-operative radiotherapy followed by cystectomy (1 female, 8 males), leaving 146 patients for whom high radiotherapy was proposed. No patient underwent radical cystectomy without pre-operative radiation. The criteria for selecting patients for radiotherapy were incomplete tumour resection, repeated relapses, large and deeply invasive tumours, tumours not suitable for transurethral resection (TUR) multiple tumours and T2 tumours grades II and III. The small number of radical cystectomies was due to a conservative surgical attitude in this period. However, this has changed in recent years.

There was a history of bladder carcinoma and previous transurethral resections in 47 patients, while another 47 had infiltrating carcinoma but no history of previous TUR. These 94 patients (64.4%) all had 1 TUR shortly before starting radiotherapy. The remainder (52 patients) did not undergo TUR and the diagnosis was established by palpation and tumour biopsy (Table 1). Staging was based on cystoscopic findings, bimanual palpation under anaesthesia, tumour biopsy and chest radiography, which were all performed shortly before the start of radiotherapy. Pre-treatment assessment also included a physical examination and standard laboratory investigations.

Clinical and pathological data are summarised in Table 1. The male/female ratio was 3.4 in the T2 and T3 categories but lower in the T4 category (1.5). The patients' mean age at the start of radiotherapy was 71.6 years (range 52–92), being highest in the T3 category (73.2 years); 83 patients (68.5%) were more than 70 years old.

The slides from 143 patients were reviewed by one pathologist (L.A.A.) with regard to histological type, grade of transitional cell carcinoma and infiltration (Mostofi, 1973). Three patients had their diagnosis cytologically confirmed.

A total of 131 patients (89.7%) had transitional cell carcinomas. Of these, 40 (30.5%) were grade II and 91 (69.5%) were grade III. There were no grade I tumours. Fifteen patients (8%) had squamous, adenocarcinoma or undifferentiated carcinomas. An increasing grade with increasing T category was observed (Fig. 1). In 135 of 143 patients (94.4%) infiltration was histologically confirmed, with the majority showing muscle invasion. In the remainder, infiltration could not be judged due to lack of stroma in small biopsy specimens.

**Table 1** Clinical and Histological Characteristics in Relation to T Category

| *Parameter* | *T category* *T2* | *T3* | *T4* | *Total* |
|---|---|---|---|---|
| No. | 35 | 61 | 50 | 146 |
| Sex | | | | |
| Male | 27 | 47 | 30 | 104 |
| Female | 8 | 14 | 20 | 42 |
| Ratio | 3.4 | 3.4 | 1.5 | 2.5 |
| Age (years) | | | | |
| Mean | 71.1 | 73.2 | 70 | 71.6 |
| Range | 54–87 | 52–92 | 54–87 | 52–92 |
| Histological type | | | | |
| TCC* WHO grade 2 | 16 | 17 | 7 | 40 |
| TCC* WHO grade 3 | 18 | 36 | 37 | 91 |
| Others | 1 | 8 | 6 | 15 |
| Infiltration confirmed | 31 | 58 | 46 | 135 |
| Surgery | | | | |
| TUR=0 | 1 | 25 | 26 | 52 |
| TUR=1 | 13 | 21 | 13 | 47 |
| TUR≥2 | 21 | 15 | 11 | 47 |
| Radiotherapy | | | | |
| Total dose (Gy) | | | | |
| <50 | 4 | 15 | 11 | 30 |
| 51–55 | 11 | 22 | 18 | 51 |
| 56–60 | 9 | 16 | 8 | 33 |
| 61–66 | 9 | 6 | 8 | 23 |
| >66 | 2 | 2 | 5 | 9 |
| Cumulative radiation effect (reu†) | | | | |
| ≤1600 | 15 | 37 | 31 | 83 |
| 1601–1700 | 4 | 6 | 6 | 16 |
| 1701–1800 | 5 | 13 | 6 | 24 |
| ≥1800 | 11 | 5 | 7 | 23 |

*TCC = Transitional cell carcinoma.
†reu = Radiation effect unit.

### *Radiation technique and treatment*

A treatment simulator was used for tumour localisation and verification of the field sizes and treatment axis. All patients were treated with megavoltage irradiation with a planned dose of either 50 Gy or 60 to 64 Gy on a cobalt-60 therapy unit or on a linear accelerator (8 MV or 25 MV). Treatment was given either with 2 opposed anterior and posterior fields, averaging 14 × 14 cm, or with 2 anterior oblique and 1 posterior field of 11 × 10 cm (a technique used only in the early phase of the study involving 11 patients with a planned dose

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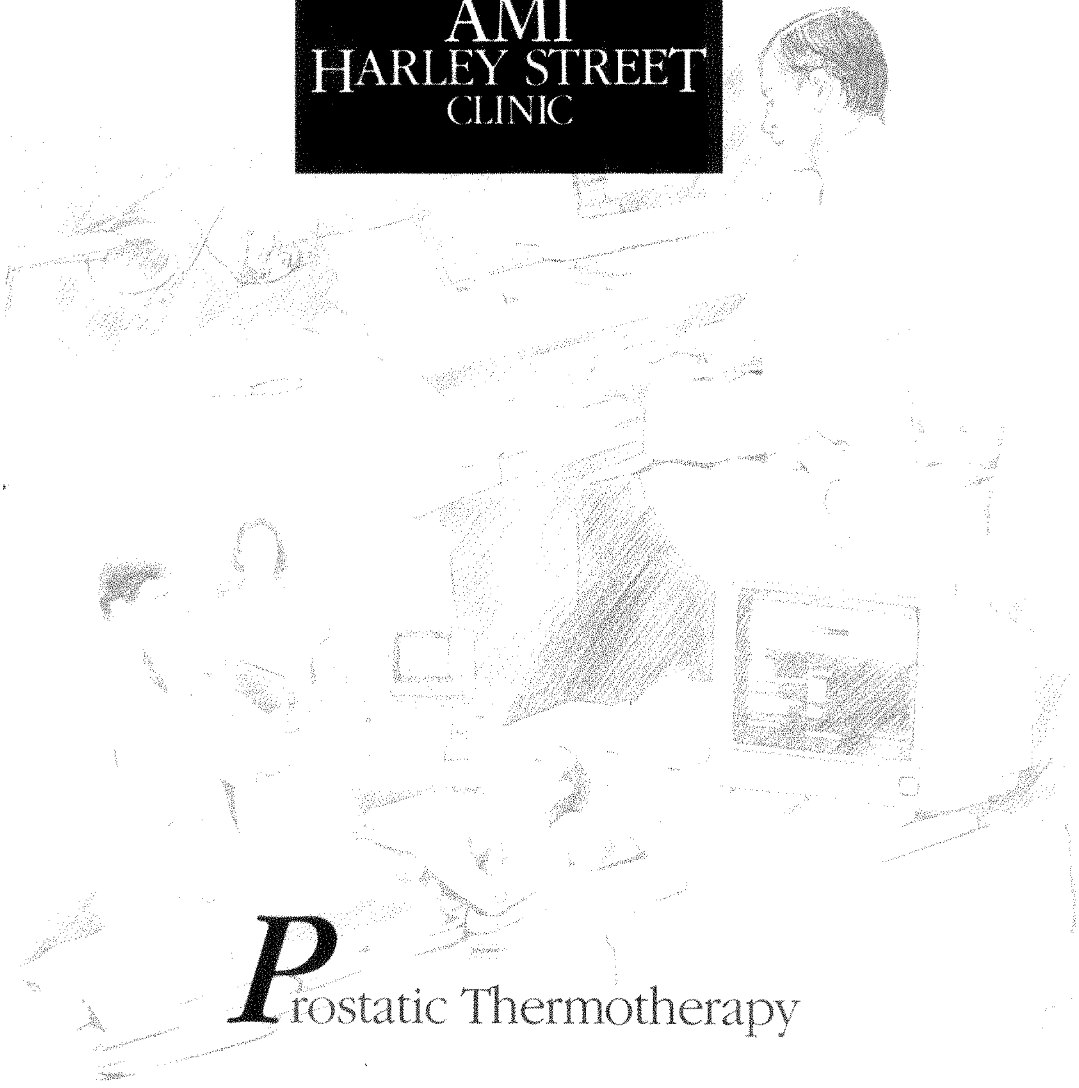

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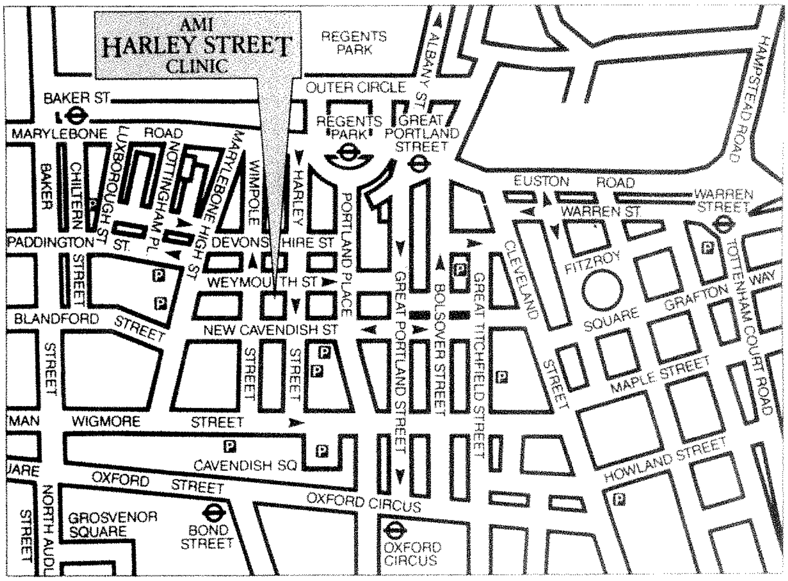

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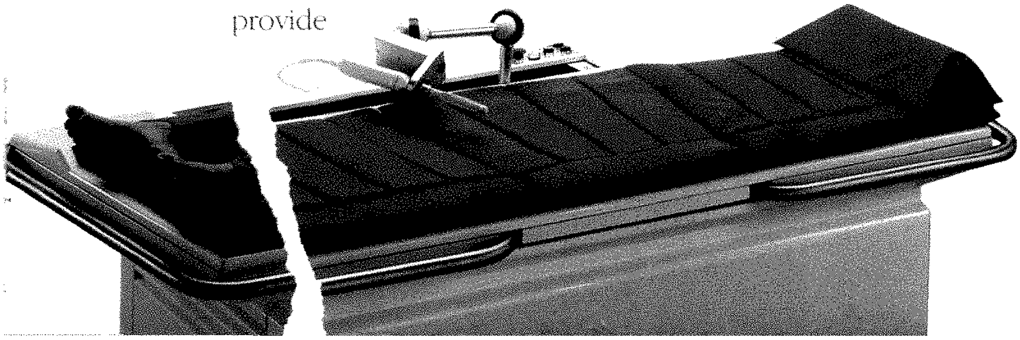

of 50–64 Gy), or with a 4-field box technique with field sizes of 13 × 13 and 13 × 14 cm. The latter technique was used if the planned dose was 60 to 64 Gy. The daily dose per fraction was 2 Gy for most patients but this varied between 1.67 and 2.9 Gy for 33 patients (in most of these cases the dose was 1.67 Gy). The effect of treatment was measured as cumulative radiation effect (CRE) according to the following formula:

$$CRE = D \times T^{-0.11} \times N^{-0.24}$$

where D was the total dose given, T the overall treatment time and N the number of fractions (Duncan and Nias, 1977). The concept of CRE makes it possible to deal with treatment gaps which may be introduced into a radiotherapy fractionation scheme either by design or inadvertently when patients need a temporary break because of acute side effects. All patients were treated 5 days per week. They were treated prone, and to avoid missing the tumour because of bladder distension, each patient voided before treatment. Of the 146 patients, 124 (84.9%) completed the planned course. Those who discontinued treatment did so because of poor tolerance or deterioration in their general condition.

*Follow-up*

This included a review of medical records until the last follow-up or death. A total of 107 patients (73.3%) were examined by cystoscopy 3 months after the end of radiotherapy to assess local response. This was defined as complete response (CR: complete macroscopic disappearance of tumour by endoscopy), partial response (PR: reduction in size of tumour), and no response (NR: either no reduction or increase in size of tumour). Chest and skeletal radiography was performed when metastases were clinically suspected. Later, the intervals between follow-up varied; 39 patients did not undergo cystoscopy following radiotherapy and others were lost to follow-up. This made it difficult to study recurrence patterns and treatment-related complications/deaths. However, 58 patients (39.7%) had only minor side effects, *e.g.* proctitis, cystitis or contracted bladder. Two patients had a severely contracted bladder.

All surviving patients were followed up until January 1986 and a few of them until September 1986. Survival was calculated from the start of radiation treatment (first analysis) and from 3 months after the end of treatment (second analysis). Patients who discontinued treatment were not excluded. All deaths (n = 126), including 15 due to intercurrent disease, were included. Time and cause of death were taken from the case notes or provided by the Cancer Registry of Norway. All patients were eligible for analysis of 5-year results.

*Statistical analysis*

Differences of distribution were evaluated by the $\chi^2$ test and variance analysis was performed to assess the relationship between local response and haemoglobin level, as well as CRE levels. The following factors were investigated with respect to survival by means of the life-table method (Dixon, 1983): sex, age, haemoglobin, erythrocyte sedimentation rate (ESR), creatinine, T category, malignancy grade (WHO), number of transurethral resections (TUR: 0 or $\geqslant 1$), time from initial diagnosis of bladder carcinoma to start of radiotherapy, radiation dose, CRE, number of radiation fields and local response. The variables were also examined by log minus log plot to see if they could be incorporated in a Cox proportional hazards regression model for survival (multivariate analysis), as potential prognostic factors or as stratifying variables (Kalbfleisch and Prentice, 1980). A forward stepwise procedure was used to include only the significant variables in the final model.

Local response was evaluated about 3 months after the end of radiation treatment. Thus 2 Cox analyses were performed; 1 did not include local response as a potential covariate at the start of radiotherapy (first analysis) and the second did include local response (second analysis).

## Results

*Local tumour regression*

Complete local tumour regression was observed in 47/107 patients (43.9%) evaluated cystoscopically for response after 3 months; 27 of these were treated with a macroscopically complete TUR (total eradication of macroscopic tumour in the bladder after transurethral resection) just before radiotherapy. Partial response was observed in 24 patients (22.4%). The complete response rate was 69.2% in T2 and 35.8% in T3/T4 categories, the difference being statistically significant ($\chi^2 = 8.93$, $P < 0.01$). There was no significant association between complete or incomplete TUR (residual tumour after transurethral resection) and local tumour regression in either T2 ($\chi^2 = 0.73$, n.s.) or T3/T4 ($\chi^2 = 0.8$, n.s.) categories.

A statistically significant difference in the complete response rate was found among patients treated with a radiation dose $<55$ Gy (28.8%) and those treated with $\geqslant 55$ Gy (58.2%; $\chi^2=9.34$, $P<0.01$). There was an even more significant difference in complete response for CRE values below and above 1700 reu: 27.1 and 75.7% respectively ($\chi^2=23.1$, $P<0.005$). Analysis of variance showed a highly significant difference in mean CRE values between the different levels of response; mean CRE levels were 1693, 1600 and 1425 reu in the complete, partial and non-responders, respectively ($P<0.0001$). No significant differences were found in mean haemoglobin values between the different levels of local response.

*Survival*

Of the 146 patients, 31 (21.1%) survived for 3 years and 20 (13.7%) survived for 5 years. The crude 5-year survival rates for patients with T2 and T3/T4 tumours were 25.7 and 9.9% respectively. Median survival was 13 months: 28 and 10 months for T2 and T3/T4 categories respectively. One T2 patient (2.9%) discontinued treatment, as did 11 T3 (18.0%) and 10 T4 patients (20.0%). This had only a slight effect on the 5-year survival rate.

Univariate survival analysis showed a significant association between survival and the following factors: age at start of radiotherapy, ESR, creatinine, T category, number of TURs (0 or $\geqslant 1$), total dose, CRE and local response (Tables 2 and 3). We found a highly significant improved survival rate for all patients with complete regression of tumour at cystoscopy 3 months after completing radiotherapy when compared with partial and non-responders ($P<0.0001$). The 5-year survival rate of the complete responders was 27.7% and for partial and non-responders it was 3.3%; 27.8% of the complete responders (n = 18) in category T2 survived for 5 years, while the 5-year survival rate for complete responders in T3 (n = 18) and T4 (n = 11) categories was 22.5 and 36.4% respectively.

Of 65 patients who were treated with radiation doses $>55$ Gy, 16.9% (11 patients) survived for 5 years (median survival 19 months).

**Table 2** Results of Univariate Analysis of Survival by Clinical and Pathological Parameters. *P* Values for Equality in Survival between Groups are Shown in the Last Column.

| *Parameter* | *No. of patients* | *% 5-year survival (No.)* | *Median survival (months)* | *Overall survival P** |
|---|---|---|---|---|
| Sex | | | | NS (0·39) |
| Males | 104 | 13.5 (14) | 16 | |
| Females | 42 | 14.3 (6) | 9 | |
| Age (years) | | | | <0.05 |
| ⩽60 | 18 | 5.6 (1) | 10 | |
| 61–70 | 50 | 20.0 (10) | 21 | |
| 71–80 | 53 | 11.3 (6) | 12 | |
| >80 | 25 | 12.0 (3) | 8 | |
| Haemoglobin (g/dl) | | | | NS (0.11) |
| ⩽12 | 52 | 11.5 (6) | 9 | |
| >12 | 85 | 14.1 (12) | 19 | |
| ESR (mm/h) | | | | <0.05 |
| ⩽30 | 65 | 16.9 (11) | 25 | |
| >30 | 56 | 10.7 (6) | 9 | |
| Creatinine (µmol/l) | | | | <0.01 |
| ⩽120 | 35 | 17.1 (6) | 16 | |
| >120 | 12 | 0.0 (0) | 7 | |
| T category | | | | <0.005 |
| T2 | 35 | 25.7 (9) | 28 | |
| T3/T4 | 111 | 9.9 (11) | 10 | |
| Histological grade | | | | NS (0.60) |
| WHO 2 | 40 | 17.5 (7) | 19 | |
| WHO 3 | 91 | 13.2 (12) | 12 | |

*Univariate analysis (Life-table method, Mantel-Cox test).
NS: Non-significant.

T category (2 levels: T2 and T3 or T4), time from diagnosis to treatment, ESR and CRE were selected as independent prognostic factors by a stepwise Cox regression analysis, with the start of radiotherapy as start time and the number of treatment fields as grouping variable. In 116 cases (79.5%), complete data were available on these variables (Table 4). Not unexpectedly, the risk of dying increased with increasing T category, with a hazard ratio of 1.8 from T2 to T3/T4 categories. The risk of dying also increased with increasing values of ESR, with a hazard ratio of 1.4 with an increase of 30 mm/h. There was also an increased risk of dying with decreasing level of CRE, with an estimated hazard ratio of 1.3 for a decreasing CRE level of 100 reu (from 1800–1700 reu). The increase in the risk of dying with increasing time from diagnosis to treatment was modest (1.2) when the difference in time from diagnosis to treatment was 1 year. Patients with 2 treatment fields seemed to have a better survival rate than those treated with 4 fields. Predicted multivariate survival curves from the first Cox model are shown in Figures 2 and 3. When local response was entered as a potential covariate, time from diagnosis to treatment, CRE, number of TURs and local response showed a significant effect on survival in the multivariate model. In 103 cases (70.5%), complete data were available on the variables under consideration. The number of treatment fields was used as a grouping variable (Table 5). As for the first Cox model, the increase in hazard ratio of increasing time from diagnosis to treatment was modest, being of the same magnitude. The hazard ratio of having no TUR versus

**Table 3** Results of Univariate Analysis of Survival by Treatment and Local Response. *P* Values for Equality in Survival between Groups are Shown in the Last Column.

| *Parameter* | *No. of patients* | *% 5-year survival (No.)* | *Median survival (months)* | *Overall survival P** |
|---|---|---|---|---|
| No. of TURs | | | | <0.05 |
| 0 | 53 | 7.5 (4) | 9 | |
| ≥1 | 93 | 17.2 (16) | 19 | |
| Time from diagnosis to radiotherapy (days) | | | | NS (0.36) |
| ≤90 | 86 | 14.0 (12) | 10 | |
| 91–180 | 11 | 18.2 (2) | 29 | |
| 181–360 | 15 | 26.7 (4) | 18 | |
| >360 | 34 | 5.9 (2) | 13 | |
| Radiotherapy (Gy) (total dose) | | | | <0.01 |
| <50 | 30 | 10.0 (3) | 7 | |
| 50–55 | 51 | 11.8 (6) | 12 | |
| 56–60 | 33 | 21.2 (7) | 25 | |
| 61–66 | 23 | 13.0 (3) | 16 | |
| >66 | 9 | 11.1 (1) | 23 | |
| Cumulative radiation effect (reu†) | | | | <0.05 |
| ≤1600 | 83 | 10.8 (9) | 9 | |
| 1601–1700 | 16 | 6.3 (1) | 10 | |
| 1701–1800 | 24 | 25.0 (6) | 28 | |
| >1800 | 23 | 17.4 (4) | 23 | |
| Local response | | | | ≤0.0001 |
| Complete | 47 | 27.7 (13) | 29 | |
| Partial | 24 | 4.2 (1) | 17 | |
| None | 36 | 2.8 (1) | 6 | |

*Univariate analysis (Life-table method, Mantel Cox test).
†reu = Radiation effect unit
NS: Non-significant.

having 1 or more TURs was 2.0. A complete local response was highly beneficial when compared with no response, with a hazard ratio of 4.6 in the no response group versus the complete response group. Predicted multivariate survival curves from the second Cox model are shown in Figure 4.

## Discussion

The complete tumour regression rate of 69.2% after 3 months in patients with T2 tumours was significantly higher than in patients with T3/T4 tumours, where the complete response rate of 35.8% was similar to that reported in other series (Wallace *et al.*, 1976; Blandy *et al.*, 1980; Quilty and Duncan, 1986). The response rate was dependent on radiation dose and CRE, but independent of whether TUR was complete or not. This is in contrast to

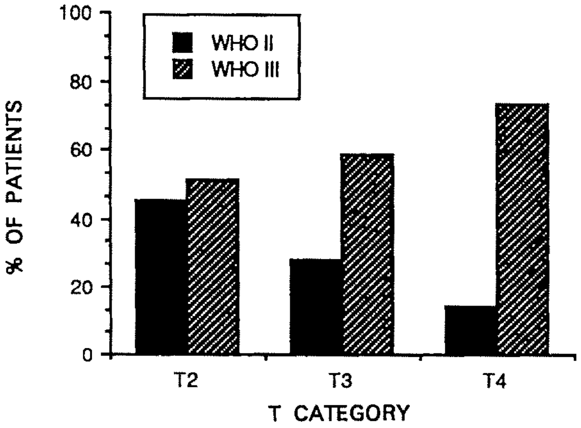

**Fig. 1** Histological malignancy grade related to T category.

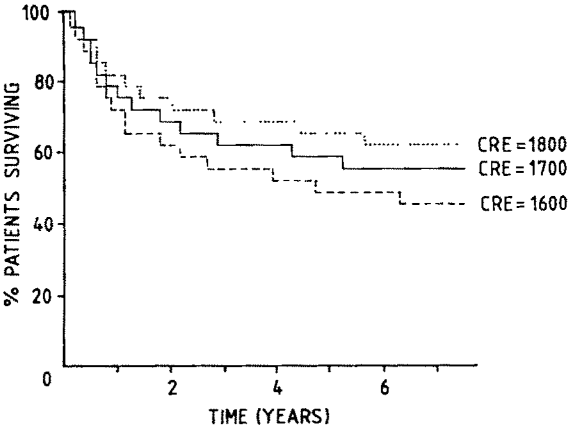

**Fig. 2** Predicted multivariate survival curves from the first Cox model with different levels of CRE in category T2 and number of treatment fields equal to 2. The other variables (sedimentation rate and time from diagnosis to treatment) are constant in all curves, and equal to the median value.

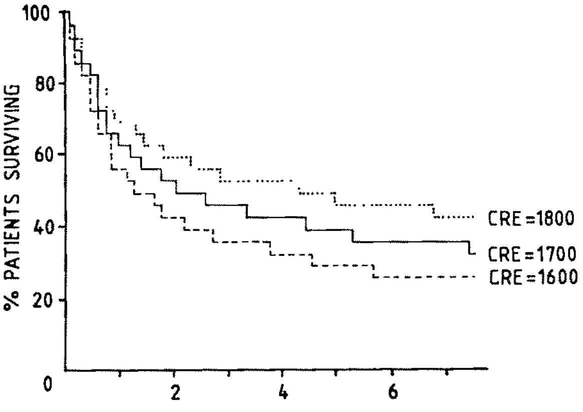

**Fig. 3** Predicted multivariate survival curves from the first Cox model with different levels of CRE in category T3/T4 and number of treatment fields equal to 2. The other variables (sedimentation rate and time from diagnosis to treatment) are constant in all curves, and equal to the median value.

**Table 4** Variables Selected in Multivariate Analysis (Cox PH model). Results for Significant Prognostic Factors are Shown (not including local response). (The estimated regression coefficients ($\beta$) show in which direction an increasing level of parameter influence on the hazard (*i.e.* risk of dying). A positive value of $\beta$ indicates a negative effect on survival (hazard function increases); a negative value of $\beta$ indicates a positive effect on survival (hazard function decreases). See text. The estimated regression coefficients with corresponding *P* values are shown in the second and last columns respectively; only variables with significant effect on survival are selected in the final model, *i.e.* the regression coefficients are significantly different from zero).

| *Prognostic factors* | $\beta$ | *S.E. ($\beta$)* | *First step unadjusted P values* | *Last step adjusted P values* |
|---|---|---|---|---|
| T category | 0.5708 | 0.2742 | 0.0196 | 0.0321 |
| Time from diagnosis to treatment | 0.0004 | 0.0001 | 0.0632 | 0.0034 |
| ESR | 0.0114 | 0.0039 | 0.0022 | 0.0045 |
| CRE | −0.0025 | 0.0007 | 0.0001 | 0.0010 |

**Table 5** Variables Selected in Multivariate Analysis (Cox PH model). Results for Significant Prognostic Factors are Shown (including local response). (The estimated regression coefficients ($\beta$) show in which direction an increasing level of parameter influence on the hazard (*i.e.* risk of dying). A positive value of $\beta$ indicates a negative effect on survival (hazard function increases); a negative value of $\beta$ indicates a positive effect on survival (hazard function decreases). See text. The estimated regression coefficients with corresponding *P* values are shown in the second and last columns respectively; only variables with significant effect on survival are selected in the final model, i.e. the regression coefficients are significantly different from zero).

| *Prognostic factors* | $\beta$ | *S.E. ($\beta$)* | *First step unadjusted P values* | *Last step adjusted P values* |
|---|---|---|---|---|
| Time from diagnosis to treatment | 0.0004 | 0.0001 | 0.0426 | 0.0390 |
| CRE | −0.0018 | 0.0008 | 0.0000 | 0.0306 |
| No. of TUR | −0.6826 | 0.2783 | 0.0640 | 0.0162 |
| Local response | −0.7629 | 0.1500 | 0.0000 | 0.0000 |

earlier reports (Rose *et al.*, 1983; Shipley and Rose, 1985) and may be explained by lack of control with the infiltrating component in an apparently complete macroscopic TUR.

A relationship between the total radiation dose delivered to the primary bladder tumour and local control of bladder carcinoma has been suggested (Morrison, 1975; Fisch and Fayos, 1976; Shipley and Rose, 1985; Quilty and Duncan, 1986). However, the only randomised trial comparing total radiation doses has shown no statistically significant difference in local control or survival, although a higher dose seemed to be beneficial (Morrison, 1975). It has been suggested that a minimum dose equivalent to 62 Gy, with conventional fractionation (CRE = 1800 reu), is necessary to achieve local control (Shipley and Rose, 1985) and it is unlikely that radiation doses <60 Gy are potentially curative when given as definitive therapy (Swanson *et al.*, 1981). In our series there was a statistically significant difference in complete response between a radiation dose <55 Gy and a dose ≥55 Gy. This

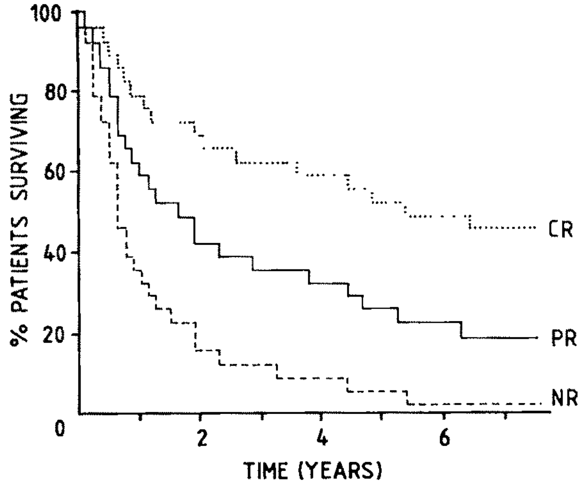

**Fig. 4** Predicted multivariate survival curves from the second Cox model for different levels of local response with number of TUR≥1 and number of treatment fields equal to 2. The other variables (time from diagnosis to treatment and CRE are constant in all curves, and equal to the median value). CR = complete response; PR = partial response; NR = no response.

difference was even more marked in relation to the radiobiological effect (CRE). Our data indicate that a radiation dose equivalent to 1700 reu may be sufficient to achieve a complete response in a relatively large proportion of patients.

Quilty and Duncan (1986) reported an increased complete response rate in patients with T3 carcinomas who had a haemoglobin level of 12 g/dl or more. We carried out an analysis of variance of our data relating haemoglobin level and degree of local response but were unable to detect any relationship.

In our series of 146 patients whose treatment was intended to cure, the overall survival rate was only 14%, compared with 36% in the series reported by Duncan and Quilty (1986). This may be partly explained by differences in the proportion of T3/T4 tumours. However, the survival figures in this study are probably less good than could be expected stage for stage in relation to the response rate at 3 months. One explanation for this discrepancy may be a lack of control with the infiltrating component in an apparently complete response by cystoscopic evaluation at 3 months.

Several studies have reported 5-year survival rates of 20 to 39% in patients with T2 and T3 tumours using full dose external beam irradiation, but local failure occurred in 40 to 50% of these (Miller and Johnson, 1973; Swanson *et al.*, 1981; Shipley and Rose, 1985). In reports showing a high 5-year survival rate, patients with a lower clinical T category may have been included, as not all of these patients had documented muscle invasion (Blandy *et al.*, 1980; Goodman *et al.*, 1981). Many of these series also included a subgroup of 10% or more who were salvaged by cystectomy (Wallace and Bloom, 1976; Shipley and Rose, 1985). In the present series, 94% of patients had histologically verified infiltration and none underwent salvage cystectomy. In patients with T4 tumours the prognosis is bad, with only 6 to 13% surviving after 5 years (Miller and Johnsen, 1973; Goffinet *et al.*, 1975; Blandy *et al.*, 1980; Hope-Stone *et al.*, 1981; Rose *et al.*, 1983). This is in accord with our own data.

In about 89% of the T2 tumours in this series, invasion was histologically confirmed. Because clinical staging has an intrinsic degree of inaccuracy (Shipley and Rose, 1985), it is possible that some of these tumours were really T3 and so they may have contributed to our relatively poor T2 survival rate of 25.7%. However, both by univariate and multivariate analysis, patients with T2 tumours had a significantly better survival than those with T3/T4 lesions. In T3 and T4 tumours, lower differentiation grades seem to provide no additional information on prognosis (Werf-Messing, 1975; Quilty and Duncan, 1986); this is in accordance with our finding of no difference in survival between histological grades 2 and 3.

A positive association between the number of TURs and survival was observed, with 1 or more transurethral resections increasing the survival time. This could be due to the fact that 51 of 52 patients (98.1%) with no previous TUR were in the T3/T4 category. However, the number of TURs proved to be an independent prognostic variable in the multivariate analysis, thus emphasising the need for tumour-reducing surgery. The result could also be partly due to an association between the number of TURs and less aggressive, more superficial tumours. On the other hand, multivariate analysis showed that a long interval between the initial diagnosis of bladder carcinoma and the start of radiotherapy was associated with reduced survival. However, this effect was very small and although statistically significant, had very little influence on the multivariate survival function. The finding is nevertheless in line with an earlier report showing that patients with a previous history of bladder cancer before entering a study had a poorer outcome (Narayana *et al.*, 1983).

Age has been identified as a significant prognostic factor in patients with a history of bladder carcinoma (Narayana *et al.*, 1983). In the present study the prognosis was worst in patients less than 60 years old and in those aged over 70. The low survival rate in the younger group may be explained by the fact that 14 of 18 patients had T3/T4 tumours. Age did not persist as an independent prognostic factor as judged by the Cox analysis.

Although radiation dose and CRE were both significant factors for survival in univariate analysis, radiation dose did not persist as an independent prognostic factor, which is in agreement with findings in earlier studies (Hope-Stone *et al.*, 1981; Duncan and Quilty, 1986). However, using the CRE formula, there was a significantly better survival rate in multivariate analysis for patients with higher CRE values (Tables 4 and 5, Figs 2 and 3). This emphasises the importance of measuring the radiobiological effect of the treatment given in order to produce an accurate analysis of survival.

In our series a highly improved survival rate was observed for T2 and T3/T4 tumours with complete regression at cystoscopy 3 months after radiotherapy (Tables 3 and 5). In fact, local response was the strongest independent parameter predicting survival. The 5-year survival of complete responders was 27.7%, compared with 4.2 and 2.8% in partial and non-responders respectively. This accords with the findings of others (Prout *et al.*, 1973; Werf-Messing, 1975; Wallace and Bloom, 1976; Blandy *et al.*, 1980; Bloom *et al.*, 1982; Herr *et al.*, 1983; Fosså *et al.*, 1985; Quilty and Duncan, 1986; Shipley *et al.*, 1987), although the survival benefit for both groups in our series was somewhat lower. Thus predictors of response to radiation were significant prognostic parameters (Shipley and Rose, 1985).

Two major concerns in the radiation treatment of elderly patients with invasive bladder cancer who are not suitable for pre-operative radiotherapy and cystectomy are curing the disease with little or no radiation-related morbidity and conserving a functioning bladder. Specific problems include diminished tolerance, slow recovery and limited life expectancy. However, this must not lead to a lower referral of these patients. Acceptably low complications have been reported after radical radiation of bladder cancer and of the whole pelvis and prostate for prostate cancer (Forman *et al.*, 1986). Concern for potential radiation-induced complications therefore does not justify withholding radiotherapy in the elderly.

Goffinet *et al.* (1975) suggested that repeat cystoscopy should be performed some weeks after 50 to 55 Gy had been delivered to the bladder and pelvis, in order to evaluate the response. If a complete response was achieved (or a partial response among those unsuited for cystectomy), full-dose irradiation could be used, with cystectomy reserved for eligible patients whose tumours had failed to respond. This concept is now being recognised, and with a synergy between chemotherapy and radiotherapy having been established, a combination of radiotherapy and chemotherapy may give an even larger number of patients the possibility of bladder-conserving treatment (Shipley *et al.*, 1987; Marks *et al.*, 1988; Porter *et al.*, 1988; Rotman *et al.*, 1988; Sauer *et al.*, 1988), in addition to reducing metastatic disease.

In conclusion, we have found that a complete response depends on achieving the maximum radiobiological effect from radiotherapy. Together with Blandy *et al.* (1980), Hope-Stone *et al.* (1981) and Quilty and Duncan (1986), we have shown that a complete response after radical radiotherapy is associated with a significantly improved survival rate. It is important to administer an adequate radiation dose over a short period of time in order to increase the possibility of both cure and long-term survival.

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# Adjuvant Topical Chemotherapy versus Immunotherapy in Primary Superficial Transitional Cell Carcinoma of the Bladder

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Summary—In a prospective randomised controlled study, the efficacy of ethoglucid was compared with that of keyhole-limpet haemocyanin (KLH) in preventing recurrent tumours following transurethral resection of primary superficial transitional cell carcinoma of the bladder. Patients treated with ethoglucid (n = 39) received 0.565 g (1% solution) ethoglucid weekly for 6 weeks and then monthly for 1 year. Patients treated with KLH (n = 38) were immunised subcutaneously with 1 mg KLH; bladder instillations of 30 mg were then given weekly for 6 weeks and thereafter monthly for 1 year.

The recurrence rates, disease-free intervals and tumour progression rates were evaluated. The end-point of the study was either progression in stage or grade or more than 1 recurrence during the observation period. The minimum length of follow-up was 1 year. The recurrence rates, mean disease-free intervals and progression rates in the 2 groups showed no statistically significant differences.

Superficial transitional cell carcinoma (STCC) of the bladder is classified in stages pTa–pT1 and grades 1–3 according to the recommendations of the International Union against Cancer (UICC, 1987) and the World Health Organisation (Mostofi, 1973). Transurethral resection (TUR) of all visible lesions with separate biopsies of the tumour margin and tumour base to confirm the completeness of resection are the first treatment modalities for STCC. Even after complete TUR, 50 to 80% of tumours recur (Cutler *et al.*, 1982; Heney *et al.*, 1982; Lutzeyer *et al.*, 1982; Dalesio *et al.*, 1983).

Adjuvant intravesical chemotherapy and immunotherapy have been advocated to reduce tumour recurrences and prolong the time to recurrence (Kurth *et al.*, 1985). Ethoglucid is one of the most frequently used cytotoxic agents (Riddle, 1973; Fitzpatrick *et al.*, 1987). There are, however, few reports on immunotherapy in bladder cancer with keyhole-limpet haemocyanin (immucocynine: Immucothel$^R$; Biosyn Technology, Stuttgart, Germany) (Klippel, 1985; Jurincic *et al.*, 1988; Kälble *et al.*, 1989; Weymann, 1989).

The aim of this study was to compare the efficacy of standard ethoglucid therapy with that of KLH immunotherapy in patients with primary STCC of the bladder.

## Patients and Methods

Histological specimens and follow-up data were available on 77 of 80 patients included in the study. After histological confirmation of stage pTa or pT1 (regardless of tumour grade), treatment began within 1 week of TUR. Group E (n = 39) received 0.565 g ethoglucid in 50 ml saline weekly for 6 weeks and then monthly for 1 year. Group K (n = 38) was immunised with 1 mg keyhole-limpet haemocyanin subcutaneously and received 30 mg (30 ml solution) weekly for 6 weeks and afterwards monthly for 1 year. TUR was performed with separate resection of the tumour base and the tumour margin to confirm the completeness of the

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**Table 1** Details of Patients

| *Treatment group* | *Males (%)* | *Age (years) (Mean ± SD)* | *Stage (%)* |  | *Grade (%)* |  |  |
|---|---|---|---|---|---|---|---|
|  |  |  | *pTa* | *pT1* | *1* | *2* | *3* |
| Ethoglucid | 69.2 | 67.3 ± 11.7 | 46.2 | 53.8 | 41.0 | 43.6 | 15.4 |
| KLH | 78.9 | 65.9 ± 12.4 | 42.1 | 57.9 | 42.1 | 47.4 | 10.5 |

Comparisons of frequencies were based on Pearson's $\chi^2$ test or Yates' corrected $\chi^2$ test ($P > 0.1$).

resection. Bladder mapping was performed in each case.

In addition to tumour stage and grade, the age and sex of the patients, multiplicity of tumours, number of bladder quadrants with visible tumour, tumour weight, dysplasia and carcinoma *in situ* (TIS) in the bladder biopsies were evaluated.

Each patient was followed up by cystoscopy every 3 months for a minimum period of 12 months (mean 26.18 ± 5.7).

The end-point of the study was progression in stage or grade or a second recurrence. In the case of a non-progressive recurrence, TUR with histological confirmation and a further 6-week course of treatment were performed. The objectives of the study were to compare the percentage of recurrences, recurrence rate, disease-free interval and tumour progression rate in both therapeutic arms.

### *Statistical analysis*

For statistical analysis BMDP statistical software (University of California) was used. The disease-free interval was defined as the interval from TUR before randomisation to the first recurrence. Curves presenting the interval to next recurrence were estimated by the Kaplan-Meier method (Kaplan and Meier, 1958).

The recurrence rate was defined as the total number of recurrences in each treatment group divided by the total number of follow-up months in each group. These results were multiplied by 100 to simplify the presentation.

The levels of significance were assessed by generalised Wilcoxon (Breslow) and generalised Savage (Mantel-Cox) tests. The Kruskal-Wallis test and Mann-Whitney U test were used as non-parametric tests for comparison of the 2 groups. Comparisons between frequencies were based on Pearson's $\chi^2$ test or Yates' corrected $\chi^2$ test.

## Results

Of 80 patients who entered the study, 77 were evaluated; 3 were lost to follow-up. The mean age of the patients was 66.6 years (range 26–83) and 74% were male; 44% of the tumours were stage pTa and 56% were pT1; 42% of the tumours were grade 1, 46% grade 2 and 13% grade 3; 66% were solitary. The mean tumour weight was 3.75 g (range 1–9). Dysplasia (grades 1–2) was found in 22% and concomitant TIS in 5% of the tumours.

The distribution of risk factors such as stage, grade, multiplicity, dysplasia and TIS in the bladder mapping in the 2 groups was comparable and showed no significant difference (Tables 1 and 2). The mean follow-up period was 26.2 months ± 5.7 with a minimum of 12 months (range 12–32).

### *Recurrences*

The overall frequency of recurrences was 33%. After ethoglucid instillation therapy the percentage of recurrences was 33% and after KLH it was 32% ($P = 0.69$). One recurrence was found in 21% of patients after ethoglucid treatment and in 26% after KLH instillation. Two recurrences were found in 13% after ethoglucid and in 5% after KLH treatment ($P = 0.47$). Multiple recurrences were found in 8% after ethoglucid and in 5% after KLH instillations ($P = 0.69$).

A recurrence with downstaging was found in 10% after ethoglucid and in 3% after KLH treatment. The rate of histological equal recurrences was 18% after ethoglucid and 26% after KLH and progression was found in 5% after ethoglucid and 3% after KLH ($P = 0.27$). The recurrence rate after

**Table 2** Risk Factors

| *Treatment group* | *Multiplicity (%)* | *Tumour weight <3 g (%)* | *Quadrant Biopsies with* |  |
|---|---|---|---|---|
|  |  |  | *DI–2 (%)* | *TIS (%)* |
| Ethoglucid | 35.9 | 59.0 | 17.9 | 7.7 |
| KLH | 31.6 | 55.3 | 26.3 | 2.6 |

Comparisons of frequencies were based on Pearson's $\chi^2$ test or Yates' corrected $\chi^2$ test ($P > 0.1$).

**Table 3** Details of Recurrences

| *Treatment group* | *Recurrences (%)* | *Multiplicity of recurrences (%)* | *No. of recurrences (%)* | |
|---|---|---|---|---|
| | | | *1* | *2* |
| Ethoglucid | 33.3 | 23.1 | 20.5 | 12.8 |
| KLH | 31.6 | 16.7 | 26.3 | 5.3 |

Comparisons of frequencies were based on Pearson's $\chi^2$ test or Yates' corrected $\chi^2$ test ($P>0.1$).

ethoglucid was 3% and after KLH 2% (Tables 3 and 4).

### *Disease-free interval*

The overall disease-free interval was 9.4 months ± 4.6 and there was no difference between the 2 groups ($P=0.86$). The mean disease-free interval after ethoglucid was 10.3 months ± 5.6 and after KLH 8.4 months ± 3.1 (Fig.).

### *Tumour progression rate*

Tumour progression was found in 4% of patients. The progression rate showed no significant difference in the treatment groups (5% after ethoglucid versus 3% after KLH). Progressions were either by stage or by stage plus grade and progression by grade alone was not observed. Comparison of the time to progression showed no statistical difference ($P=0.57$ Mantel-Cox test).

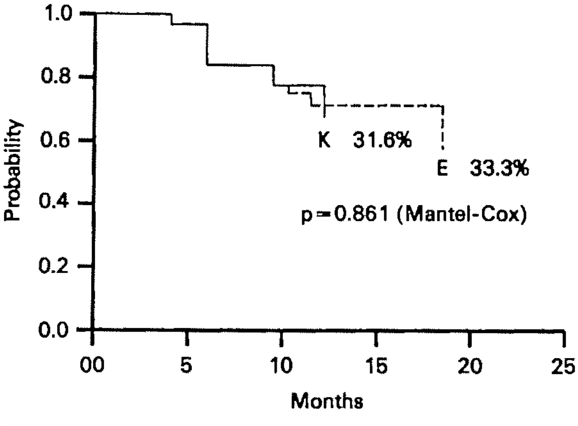

**Figure** Comparison of Kaplan-Meier curves for time to recurrence. K: KLH group. E: Ethoglucid group.

After histological confirmation of progression or a second recurrence, treatment was changed to intravesical instillations of Bacillus-Calmette Guérin (BCG), systemic chemotherapy or operative treatment according to the nature of the progression and the age of the patient.

### *Side effects*

No severe side effects were found in either of the 2 groups. Chemocystitis was noted in 5 of 39 patients (13%) in the ethoglucid group but in none of the KLH patients. This was not severe and it was not necessary to interrupt treatment. In the KLH group, 3 patients (8%) had a febrile reaction for 1 or 2 days. No systemic side effects were reported.

## Discussion

Ethoglucid is a well known and well documented alkylating cytotoxic agent (Riddle, 1973; Smith *et al.*, 1978; Fitzpatrick *et al.*, 1987). Chemocystitis and the possible development of bladder contracture or reflux in about 4% of patients are the limiting factors in the long-term use of the drug (Smith *et al.*, 1978; Virdi, unpublished data). It is of interest to investigate drugs with similar or greater efficacy which lack the side effects of cytotoxic drugs. BCG

**Table 4** Recurrence Rates, Follow-up, Disease-free Intervals and Progression Rates

| *Treatment group* | *Recurrence rate (%)* | *Follow-up (months) (Mean ± SD)* | *Disease-free interval (months) (Mean ± SD)* | *Tumour progression (%)* |
|---|---|---|---|---|
| Ethoglucid | 2.79 | 26.6 ± 6.0 | 10.3 ± 5.6 | 5.1 |
| KLH | 2.33 | 25.8 ± 5.3 | 8.4 ± 3.2 | 2.6 |

Recurrence rate = number of recurrences divided by the total number of follow-up months multiplied by 100.
Disease-free interval = time to first recurrence.

has a high rate of side effects (Brosman, 1982; Lamm *et al.*, 1982). Keyhole-limpet haemocyanin is a powerful immunogenic compound of high molecular weight (Jurincic *et al.*, 1988). The systemic and topical use of KLH in experimental studies has been shown to reduce tumour growth in animals (Lamm *et al.*, 1981). There are few data on the efficacy of KLH in the prophylactic treatment of patients with STCC. In a prospective randomised trial of KLH and mitomycin C, there was a recurrence rate of 14.2% in the KLH group (mean follow-up 20.7 months) and 39.1% in the mitomycin C group (mean follow-up 18.3 months) ($P<0.05$) (Jurincic *et al.*, 1988). Other studies (Jurincic, unpublished data) showed a recurrence rate of 28% after a mean follow-up of 24 months for KLH-treated STCC and 31.5% after a mean follow-up of 35.2 months. We therefore started this prospective randomised trial to compare KLH with standard chemotherapy. The results showed no difference between the 2 therapeutic arms.

The results in both groups suggest that there is no difference in the efficacy of the 2 treatments but this cannot be confirmed until a much larger trial has been carried out. The precise mechanism of action of KLH remains unknown, but it is known that its strong antigenic effect induces a primary antibody response in man (Lamm *et al.*, 1981). However, the lack of side effects with KLH when compared with other immunotherapeutic agents and its efficacy support its use. The excellent results obtained when it was compared with mitomycin C (Jurincic *et al.*, 1988) could not be confirmed in the present study.

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# Short-term Radiotherapy as Palliative Treatment in Patients with Transitional Cell Bladder Cancer

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Summary—We report the results and complications of treatment with palliative, short-term radiotherapy in 162 elderly or disabled patients. Improvement in tumour-associated symptoms was noted in 75 of these patients and 72 survived for more than a year. Those who responded to radiotherapy had a 5-year cancer-free survival rate of 58% compared with 4% in patients who did not respond to treatment. Survival was also affected by stage and indications for radiotherapy. In 85 patients without severe symptoms, where the tumour was judged curable but the patient was unsuitable for a full course of radiotherapy, the 5-year cancer-free survival rate was 21%, which is in accordance with what can be achieved with full-course radiotherapy; 42% had various minor acute side effects. The 5-year late complication rate was 7%.

Radical radiotherapy has for many years been the treatment of choice for invasive bladder cancer when radical surgery is ruled out by old age or poor health (Edsmyr *et al.*, 1978; Hope-Stone *et al.*, 1981). Survival after radiotherapy alone, however, is relatively short (approximately 25% for T2–T3 tumours) (Wallace and Bloom, 1975; Miller, 1980), although an initial response is seen in about 50% of patients (Blandy *et al.*, 1980; Jenkins *et al.*, 1988). Furthermore, treatment with radiotheray is associated with major side effects and, for elderly patients, a full course is a lengthy and tiring experience.

In an attempt to provide palliation in elderly patients not considered fit enough for radical treatment, a new treatment was introduced in Stockholm in 1974. A short-term course of radiotherapy (7 Gy 3 times over 5 days) was given to a total dose of 21 Gy. This report summarises our experience with patients treated between 1974 and 1986.

## Patients and Methods

Over a 12-year period (1974–1986), 162 patients were treated (94 men and 68 women). Their mean age was 78 years (range 54–96). The patients were diagnosed at 4 different Stockholm hospitals and treated at Radiumhemmet, the centre for oncology in the Stockholm area. Follow-up was extended through 1988.

All tumours were of transitional cell origin but 4 also had a squamous cell component; 103 patients had primary tumours and 59 had recurrences of previously resected tumours. The distribution of grade and stage is presented in Table 1. All but 4 tumours were invasive. One patient (aged 83 years) had a carcinoma *in situ* and was unable to tolerate intravesical therapy. Another patient (aged 86 years) had an exophytic tumour and a concomitant carcinoma *in situ*. A third patient (aged 87 years) had multiple tumours which were impossible to resect transurethrally. The remaining patient, 86 years old, had recently had a myocardial infarction, rendering anaesthesia impossible Nineteen patients had T1 tumours. Only 3 were primary and all patients had intolerable symptoms. The remaining 16 had frequent recurrences (multiple tumours in 11 and concomitant carcinoma *in situ* in 3).

Although the general intention was to provide palliation, the tumour was judged curable but the

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**Table 1** Distribution by Stage and Histological Grade

| | *Stage* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Tis* | *Ta* | *T1* | *T2* | *T3* | *T4* | *Total* |
| Grade 2 | | 1 | 3 | 6 | 3 | 3 | 16 |
| Grade 3 | 1 | 2 | 16 | 26 | 70 | 31 | 146 |
| Total | 1 | 3 | 19 | 32 | 73 | 34 | 162 |

Eleven patients had a concomitant carcinoma *in situ* and 4 had an additional squamous cell cancer component.

patient unsuitable for full-course irradiation in as many as 85 patients without severe symptoms. The reasons for not giving a full course were advanced age or poor general health. No consistent screening for metastatic disease was attempted. The indications for radiotherapy are presented in Table 2, where patients have been classified into various stages. The mean age was highest in patients considered curable (79 years). Various stages, however, had a similar distribution regardless of the indications for radiotherapy.

Radiation was given on 3 occasions over a 5-day period; 8 MeV photons were used from anterior and posterior opposing fields with a 12 × 15 cm field size, to a total dose of 21 Gy in the middle of the pelvis calculated from the anterior-posterior distance. In 8 patients radiation was repeated 6 to 12 months later and 1 patient received 3 courses of 21 Gy.

It was intended that the first endoscopic check-up should be performed 3 months after completion of irradiation, but deterioration in health or progression of cancer made this impossible in 57 of the 162 patients (35%).

For statistical calculation of survival and late complication rates, life-table methods were used and differences between groups of possible prognostic value were calculated with the Log Rank test (Peto *et al.*, 1977). Relative survival implies cancer-free survival. Deaths from causes other than cancer were considered to be censored observations.

## Results

### *Local response*

Thirty-nine of the 162 patients (24%) showed a complete clinical response with no evidence of tumour at 3 months. Two tumours were grade 2 and 37 were grade 3. The distribution of stages for these 39 patients is shown in Table 3. Seventeen patients had a later recurrence. In 2 cases radiation was repeated but without further effect.

Persistent tumour after radiotherapy was seen in 123/162 patients (76%). This number includes those patients who did not have an endoscopic check-up at 3 months; 13 tumours were grade 2 and 110 were grade 3. Tumour stages are shown in Table 3.

A chi-squared test, carried out on response to therapy by tumour stage, showed a significant difference only between T2 tumours and T3+T4 tumours ($P=0.052$).

Six patients with persistent tumour received a second course of radiation and 1 underwent 3 courses. In no case were the tumours affected by the repeated treatment.

**Table 2** Indications for Radiotherapy

| *Indication* | *Tis* | *Ta* | *T1* | *T2* | *T3* | *T4* | *Total* |
|---|---|---|---|---|---|---|---|
| Cure (mean age 79) | | 1 | 10 | 22 | 39 | 13 | 85 |
| Bleeding (mean age 78) | | 1 | 4 | 9 | 29 | 9 | 52 |
| Local symptoms (mean age 74) | 1 | 1 | 5 | 1 | 5 | 12 | 25 |
| Total | 1 | 3 | 19 | 32 | 73 | 34 | 162 |

**Table 3** Local Response to Radiotherapy at 3 Months in Various Stages

| | *Stage* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Tis Ta T1* | *T2* | *T3* | *T4* | *Total* | *T3+T4* | *T2–T4* |
| No tumour | 5 | 12 | 15 | 7 | 39 | 22 | 34 |
| Residual tumour | 18 | 20 | 58 | 27 | 123 | 85 | 105 |
| Total | 23 | 32 | 73 | 34 | 162 | 107 | 139 |

### *Survival*

Patients who responded to radiotherapy had a relative 5-year survival rate of 58% compared with 4% in those who failed to respond ($P<0.001$) (Fig. 1).

There was a significant difference in survival between the various stages ($P<0.001$) (Fig. 2). However, among patients who were tumour-free at 3 months, no difference in survival between different stages was noted ($P=0.762$), in contrast to those unresponsive to radiotherapy ($P<0.001$).

No difference in survival rate was observed when the following variables were analysed: age, sex, grade or whether the tumour was primary or recurrent.

There was, however, a significant difference in the survival rate depending on the indication for radiotherapy ($P<0.001$) (Fig. 3). The relative 5-year survival rate for the 85 patients with tumours considered to be curable was 21%, compared with 6% for patients with bleeding and 0% for patients with other local symptoms. The 3 groups had a similar distribution of stages, but age was lower and there were fewer primary tumours in the group with serious local symptoms (Table 2). Within the group of 85 patients treated with a view to eventual cure, there was no significant difference in survival when analysing stage ($P=0.167$), age ($P=0.93$), or whether the tumours were primary or recurrent ($P=0.925$).

### *Palliation*

Improvement in tumour-associated symptoms was noted in 75 patients, although not more than 39 of the 162 patients were tumour-free 3 months after completion of radiotherapy. Among patients treated for bleeding, 27 showed improvement in symptoms or stopped bleeding. Severe local symptoms either improved or disappeared in 14 of 25 patients who were treated mainly because of these symptoms. Although palliation was the main objective, results were sometimes hard to assess because of insufficient information. In addition, as many as 72 of the 162 patients survived for more than 1 year.

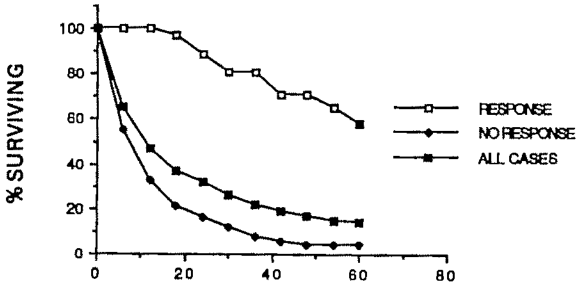

**Fig. 1** Relative survival according to response to local radiation in 162 patients treated with short-term radiotherapy. Log Rank test for trend: $P<0.001$.

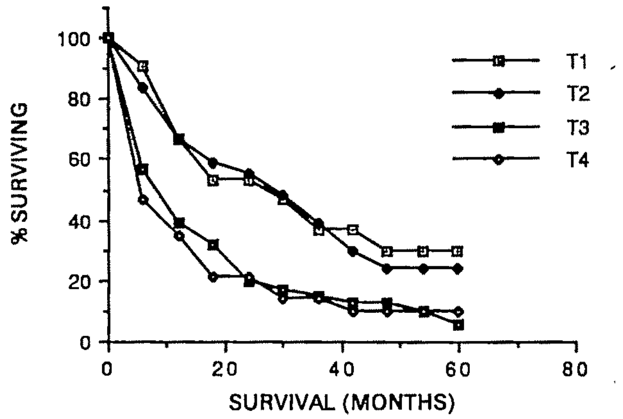

**Fig. 2** Relative survival according to clinical stage in 162 patients treated with short-term radiotherapy. Log Rank test for trend: $P<0.001$.

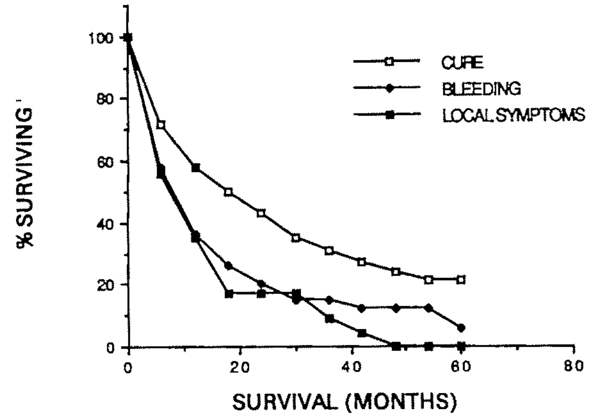

**Fig. 3** Relative survival according to indications for therapy. Log Rank test for trend: $P<0.001$.

### *Complications*

Of the 162 patients, 68 (42%) suffered acute side effects, usually of minor degree (Table 4). Diarrhoea and painful micturation predominated and lasted for 1 to 3 months. Data on side effects were lacking in 64 patients, making evaluation unreliable. Late serious complications were seen in 5 patients (3%). They occurred in the first 3 years after treatment and the late 5-year complication rate, calculated

**Table 4** Complications of Radiotherapy

| | *Acute* | *Late* | *Total* |
|---|---|---|---|
| No complication | | | 25 |
| Bladder only | 12 | 1 | 13 |
| Bowel only | 33 | 3 | 36 |
| Bladder and bowel | 18 | 1 | 19 |
| Other | 5 | | 5 |
| Not stated | | | 64 |
| Total | 68 | 5 | 162 |

with life-table methods, was 7%. Two patients required a colostomy and 1 required urinary diversion. One of these patients had received a second course of radiotherapy 8 months after the first. Apart from that case, only minor acute side effects were seen in the 9 patients who received more than 1 course of radiotherapy.

## Discussion

Invasive bladder cancer that is not amenable to radical surgery has a poor prognosis and often gives rise to severe local symptoms. Radical radiotherapy is usually the treatment of choice but is not always feasible for elderly or disabled patients. The overall 5-year survival rate following radical radiotherapy has been reported to be approximately 25%, with an initial tumour response of just below 45% (Wijkström *et al.*, 1987).

In this series of elderly patients, where palliation was the main objective, the mean age was 78 years, which is about 10 years more than that usually seen when full-dose radiotherapy is given. Short-term therapy, given 3 times over 5 days, is time-saving both for the patient and the unit. The dose of 21 Gy given in 3 fractions over 5 days also corresponds theoretically to the normal fractionation of 36 Gy given in 18 fractions over 24 days (Thames and Hendry, 1987).

A 5-year relative survival rate of 14% was seen in this series, together with an initial tumour response rate approximately half of that seen in radically irradiated patients (24%). These figures are similar to those reported in other series with palliative pelvic radiotherapy (Mameghan and Fisher, 1989). However, about half of our patients did not have severe symptoms and the tumour was considered curable, although the patient was unsuitable for a full course of radiotherapy. It is noteworthy that these 85 patients, with a stage distribution similar to that of the whole series and treated with a view to cure, had a relative 5-year survival rate of 21% and an initial tumour response rate of 36%. This is similar to that seen with full-course radiotherapy. It is also significant that, among patients showing an initial response to radiation, the relative 5-year survival rate was 58%.

Although palliation was our main aim, this was more difficult to assess retrospectively than survival. An improvement in symptoms was noted in about half of the patients, but data were either unreliable or completely lacking.

Early complications were seen in 43% of patients and late complications in 3%, associated with irradiation of the rectum. Many radiation-related complications have a latent period of months to years and adjustments must be made to exclude patients who no longer run the risk of developing late complications, especially when life expectancy is short. For this reason, an actuarial method of reporting these complications should be used (Abratt, 1983). The risk of developing serious late complications was, in this series, calculated at 7% in 5 years.

Seven patients received a second and 1 a third course of 7 Gy × 3 after 6 to 12 months without further complications (but with no effect on the tumour). One patient who received a second course required a colostomy because of rectal damage. Complications occurred when 2 opposing fields were used. A better dose distribution for this short-term radiotherapy is now in use with an isocentric technique involving 3 treatment portals (1 anterior and 2 oblique fields with a wedge from behind) and is similar in principle to the full-dose radiotherapy given to bladder cancer patients.

Short-term radiotherapy (7 Gy × 3 over 5 days) was intended exclusively for palliation of severe symptoms and it has now become an established form of treatment in our clinical practice. The results, however, especially the impact on cancer-free survival, were unexpected and we feel they are most gratifying in these patients with a short life expectancy where conventional aggressive treatment is not appropriate.

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# Quantitative Analysis of the Accuracy of Linear Array Transrectal Ultrasound in Measurement of the Prostate

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Summary—In 61 prostate autopsy specimens, linear array transrectal ultrasound and electronic vernier calipers were used to measure 3 maximal diameters along the longitudinal, anterior-posterior and transverse axes. The results were comparable. We assessed the reliability of empirical formulae, derived from various combinations of these 3 diameters, for the prediction of prostatic volume and weight. Formulae using all 3 diameters were accurate. The combination of longitudinal and anterior-posterior diameters, which was used clinically for prostate measurement, was less accurate.

Prostatic hypertrophy is not uncommon in the Hong Kong Chinese. Even though local clinical experience confirmed it as a common cause of admission to surgical wards, data tended to concentrate on the histological aspects. Studies on size were not available (Brelow and Chan, 1977) and this can be ascribed partly to a lack of convenient quantitative measuring devices.

Prostate size has been estimated by various methods, including cystourethrography, urethrocystoscopy and urethral pressure profile, all of which have proved to be inaccurate (Vilmann *et al.*, 1987). Rectal digital examination is convenient but requires adequate exposure to enucleated specimens to be accurate, and even so was judged unreliable for large prostates (Watanabe *et al.*, 1974).

Ultrasound has become increasingly popular in the measurement of prostate size, as have transabdominal and transrectal or transurethral tomographic sector scanners (Kimura *et al.*, 1986; Ohishi, 1987). However, the accuracy of linear transrectal scanners has seldom been assessed in relation to prostatic measurement, and tomographic procedures cannot be applied directly.

In addition, many formulae for estimating prostatic size approximated the prostate to simple geometric shapes and were not empirically derived. Of those that were empirically derived, tissue specimens were often obtained during suprapubic or transurethral prostatectomy, with inevitable loss of tissue during resection and a variable amount of residual prostatic tissue remaining after the operation (Rasmussen, 1975; Smith and Haveland, 1982). To avoid tissue loss, Vilmann *et al.* (1987) studied 26 autopsy specimens but used transabdominal sector scanners and, once again, a mathematical approximation to the ellipsoid shape.

The present study was therefore performed on autopsy specimens and empirically derived formulae were obtained from linear array transrectal ultrasound measurements. Since only 2 diameters can be conveniently measured with most scanner types in a single picture, we also tried to assess the reliability of calculating prostate size using 2 diameters.

## Materials and Methods

Between January and May 1988, 61 autopsy specimens were removed from patients without prostatic pathology. The prostates were weighed and their volume measured by the water displacement method. They were than carefully mounted (with the rectal side vertical) in a water bath filled with normal saline using long metal pins.

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**Table 1** Summary of Data

| | | *Mean* | *Minimum* | *Maximum* | *Standard deviation* |
|---|---|---|---|---|---|
| Age (years) | A | 64.5 | 19 | 89 | 16.64 |
| Longitudinal diameter | Lu* | 4.34 | 3 | 5.4 | 0.536 |
| | Lc | 4.36 | 3.4 | 5.0 | 0.431 |
| Transverse diameter | Wu | 3.31 | 2.1 | 4.5 | 0.507 |
| | Wc | 3.15 | 2.2 | 4.3 | 0.471 |
| Anterior-posterior diameter | Tu | 2.26 | 1.4 | 3.4 | 0.418 |
| | Lc | 2.47 | 1.7 | 3.4 | 0.422 |

N.B. This summary is based on 55 sets of data, after discarding 6 outliers.
* See text for abbreviations.

**Table 2** Correlation Matrix of all Data

| | *Age* | *Weight* | *Volume* | *Lu* | *Wu* | *Tu* | *Lc* | *Wc* |
|---|---|---|---|---|---|---|---|---|
| Weight | 0.158 | | | | | | | |
| Volume | 0.174 | 0.991 | | | | | | |
| Lu | 0.144 | 0.516 | 0.523 | | | | | |
| Wu | 0.229 | 0.638 | 0.636 | 0.443 | | | | |
| Tu | 0.294 | 0.770 | 0.793 | 0.448 | 0.487 | | | |
| Lc | 0.049 | 0.637 | 0.618 | 0.756 | 0.342 | 0.462 | | |
| Wc | 0.245 | 0.791 | 0.796 | 0.418 | 0.808 | 0.641 | 0.401 | |
| Tc | 0.220 | 0.853 | 0.857 | 0.460 | 0.510 | 0.818 | 0.547 | 0.645 |

An Aloka Echocamera LS SSD-248 model ultrasound with a linear array transducer (Model No. UST-658-5, frequency 5 MHz) was used to measure the maximal longitudinal (L), anterior-posterior (T) (along the midline sagittal plane of the urethra) and the transverse diameter (W) (along the transverse section of the prostate at right angles to the above plane). The criteria for judging the sagittal plane of the urethra were the same as *in vivo*, and this was done by 2 workers (Y.L.Y. and M.L.L.) with experience in approximately 5000 cases of general ultrasound and 300 cases of linear transrectal ultrasound. After the ultrasound measurements were made (Lu, Tu, Wu), electronic vernier calipers were used to measure the prostate at the closest possible sites to those measured by ultrasound in order to obtain Lc, Tc and Wc.

All of the above data, including the age of the patient, were analysed using a VAX minicomputer and a standard statistical package (SAS).

## Results

A summary of the data is shown in Table 1. Correlation matrix analysis (Table 2) showed little correlation between the diameters themselves, and amongst diameter, age, volume and weight. Correlation of volume with weight was very high (correlation coefficient 0.991) with calculated density close to 1. Thus it is reasonable to use all formulae on weight to reflect volume, and *vice versa*.

There was a strong relationship between the 2 methods of measurement (between Lu and Lc, r = 0.756; Wu and Wc, r = 0.808; Tu and Tc, r = 0.818). Linear regression analysis of the scatter diagrams plotting the corresponding measurements (Table 3) again demonstrated that ultrasound values were very close to caliper values, except that ultrasound slightly overestimated W and underestimated T.

**Table 3** Mathematical Analysis of Correlation of the 2 Methods of Measurement

| *Regression equation* | $R^2$ *(%)* | *Maximum absolute error* | *Maximum relative error (%)* |
|---|---|---|---|
| Lu = 0.248 + 0.940 Lc | 57.1 | 0.2 | 4.6 |
| Wu = 0.568 + 0.870 Wc | 65.3 | 0.2 | 6.4 |
| Tu = 0.273 + 0.810 Tc | 67.0 | 0.2 | 8.1 |
| M = 1.680 + 1.004 V | 98.2 | 0.65 | 3.1 |

**Table 4** R-square Value of Various Possible Regressor Combinations in Reflection of Volume (V)

| *Regressor combination* | *R-square for V (%)* | *Regressor combination* | *R-square for V (%)* |
|---|---|---|---|
| Lu | 26.0 | Lc | 37.1 |
| Wu | 39.3 | Wc | 62.6 |
| Tu | 62.2 | Tc | 72.9 |
| Lu, Wu | 45.7 | Lc, Wc | 73.0 |
| Lu, Tu | 65.1 | Lc, Tc | 75.8 |
| Wu, Tu | 69.9 | Wc, Tc | 82.9 |
| Lu, Wu, Tu | 70.6 | Lc, Wc, Tc | 85.1 |

To select the best subset of diameters for predicting the volume V and weight M, regression equations with all possible combinations of 1, 2 and 3 diameters of both methods of measurement were derived. Their corresponding accuracy as reflected by R square is listed in Table 4. The most accurate were the 3-diameter combination formulae (r-square 70–85%), while the 2-diameter combinations were less accurate (r-square 45–83%). The best 2-diameter ultrasound combination was Wu plus Tu (r-square 70%), which was very close to the 3-diameter methods. These are the sets of diameters measured by tomographic scanners. The next best were Lu plus Tu, the diameters measured with linear array scanners clinically (r-square 65%). The corresponding empirically derived formulae were:

V (volume) $= 2.59\,Lu + 11.1\,Tu - 17.0$
M (weight) $= 2.67\,Lu + 10.8\,Tu - 15.1$.

As in any geometrical model, volume should be proportional to the product of the 3 diameters, and so we regressed the logarithms of the volume against the logarithms of the diameters (Tables 5A and B).

**Table 5A** Regression Equations for Weight (M) using Various Combinations of Diameters

1. $M = -6.91 + 6.45\,Lu$
2. $M = -6.81 + 8.45\,Wu$
3. $M = -6.94 + 12.4\,Tu$
4. $M = -17.0 + 3.63\,Lu + 6.74\,Wu$
5. $M = -15.1 + 2.67\,Lu + 10.8\,Tu$
6. $M = -15.9 + 4.56\,Wu + 9.67\,Tu$
7. $M = -19.8 + 1.59\,Lu + 4.07\,Wu + 9.05\,Tu$
8. $M = -22.0 + 9.90\,Lc$
9. $M = -14.4 + 11.3\,Wc$
10. $M = -12.3 + 13.5\,Tc$
11. $M = -33.3 + 5.92\,Lc + 9.10\,Wc$
12. $M = -23.6 + 3.79\,Lc + 11.4\,Tc$
13. $M = -20.4 + 5.89\,Wc + 9.31\,Tc$
14. $M = -30.0 + 3.36\,Lc + 5.63\,Wc + 7.62\,Tc$

**Table 5B** Regression Equations for Volume (V) using Various Combinations of Diameters

1. $V = -8.67 + 6.45\,Lu$
2. $V = -8.12 + 8.31\,Wu$
3. $V = -9.14 + 12.6\,Tu$
4. $V = -18.5 + 3.70\,Lu + 6.58\,Wu$
5. $V = -17.0 + 2.59\,Lu + 11.1\,Tu$
6. $V = -17.6 + 4.28\,Wu + 10.0\,Tu$
7. $V = -21.4 + 1.58\,Lu + 3.79\,Wu + 9.42\,Tu$
8. $V = -22.0 + 9.49\,Lc$
9. $V = -15.9 + 11.2\,Wu$
10. $V = -13.8 + 13.4\,Tc$
11. $V = -33.4 + 5.47\,Lc + 9.18\,Wc$
12. $V = -23.5 + 3.28\,Lc + 11.6\,Tc$
13. $V = -21.8 + 5.85\,Wc + 9.23\,Tc$
14. $V = -30.0 + 2.86\,Lc + 5.63\,Wc + 7.79\,Tc$

**Table 5C** Regression Equations for Volume (V) using Various Combinations of Diameters

| | *Adjusted r* |
|---|---|
| 1. $\ln V = 0.66 + 1.54 \ln Lu$ | 0.312 |
| 2. $\ln V = 1.35 + 1.32 \ln Wu$ | 0.351 |
| 3. $\ln V = 1.75 + 1.44 \ln Tu$ | 0.624 |
| 4. $\ln V = 0.32 + 1.00 \ln Lu + 0.95 \ln Wu$ | 0.452 |
| 5. $\ln V = 0.95 + 0.66 \ln Lu + 1.23 \ln Tu$ | 0.665 |
| 6. $\ln V = 1.16 + 0.67 \ln Wu + 1.19 \ln Tu$ | 0.693 |
| 7. $\ln V = 0.72 + 0.48 \ln Lu + 0.56 \ln Wu + 1.09 \ln Tu$ | 0.665 |

However, the corresponding values of r-square were not improved relative to those obtained without taking logarithms. The latter were obviously much easier to use in practice (Table 5C).

The ellipsoidal model has often been used to calculate prostate volume (Vilman *et al.*, 1987) (formula $= 4/3\,\pi.\ 1/8$ L.W.T). However, it proved to be less satisfactory than our derived formula, differing significantly from the measured volume at the 0.001 level ($t = 3.66$). thus it was concluded that our derived formula reflected the true volume more accurately.

## Discussion

Our results have shown that volume and weight data correlated well and could be interchanged. As expected, there was an overall greater accuracy of volume for both methods of diameter measurement. The fact that prostatic enlargement and difficulty with micturation due to urethral deformity are primarily functions of volume changes leads us to suggest that volume is a better assessment criterion than weight.

Our individual linear array ultrasound diameter measurements were very accurate when compared with those of calipers, supposedly the gold standard. The combination of Lu and Tu, although not the best, still attained 65% r-square value for volume measurement, compared with the 70.6% of the 3-diameter ultrasound formula. Since these are the values we measured in clinical practice with linear array transducers (Wu being inconvenient to measure), our approach using these 2 diameters appears practical for the calculation of approximate prostate volume. The formula was complicated but could be incorporated into existing routine ultrasound programmes to display the volume. Our experience in similar online analysis of blood gas has shown this to be a convenient approach for complicated formulae and it avoids the necessity for manual input of data (Yip, 1987).

For predicting volume accurately from a single diameter, the anterior-posterior diameter (T) was the best and exceeded the other 2 diameters combined (Lu and Wu) in accuracy (62 versus 46% for volume and 59 versus 46% for weight). The same phenomenon was not observed in diameters measured by calipers.

For both methods of measurement, accuracies were in the following order: longitudinal < transverse < anterior-posterior (Lu < Wu < Tu). Scattergrams of Lu, Wu and Tu versus weight and volume also revealed progressive scattering of points as the magnitude of diameter increased, again in the order of (Lu > Wu > Tu). As the limit of accuracy of calipers and ultrasound cursors is fixed (around ±0.01 cm) and the absolute magnitude of diameter is Lu > Wu > Tu, the systemic fractional error of measurement should be the opposite way round. This apparent paradox can only be explained by the higher probability of incorrectly measuring the longer diameters. This was in fact our unanimous impression formed during measurement. Because of the irregular shape of the prostate, fixing the measurement axis is more difficult with longer measured length both *in vivo* and *in vitro*, regardless of the type of ultrasound scanner. This probably explains the observation of progressive scattering of estimated sizes as the true prostate size increased (Watanabe *et al.*, 1975).

Digital assessment of prostatic size has often been criticised. In our case, the r-square value of the transverse diameter alone in assessment of volume was only 40%. As this was performed using ultrasound, it is good mathematical proof of the unreliability of digital examination.

We were concerned about whether the impressions gained during autopsy ultrasound measurement could be extrapolated to the *in vivo* situation and we now believe that this is possible. We have performed at least 1000 transrectal ultrasound measurements and our ultrasonic settings were similar to those of our autopsy measurements. The only difference was the absence of the rectal wall in the latter. We carried out small scale trials with a thin rectal wall intervening and found that it made no difference to the ultrasound values, but did make the procedure much more difficult.

Another concern may be the difference in size after fixation of the specimen. We also made measurements before and after fixation and calculations showed that the contraction was fairly homogeneous. However, conversion of our formula back to the unfixed tissue size involved another formula, rendering this approach impractical.

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# Activation of Complement, Kallikrein-kinin, Fibrinolysis and Coagulation Systems by Urinary Catheters. Effect of Time and Temperature in Biocompatibility Studies

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Summary—Urethral strictures induced by the use of latex catheters and combined silicone/latex catheters following open-heart surgery have been reported. These strictures differ from the post-catheterisation type in affecting a greater length of urethra. Recently it was shown that complement was activated by catheters which cause inflammation, in contrast to clinically silent catheters. The present study was designed to investigate a possible association between catheter-induced inflammation and activation of another mediator of inflammation, the contact system. We also investigated various *in vitro* conditions to optimise biocompatibility studies. Our data indicate that both the complement and the kallikrein-kinin system are activated by potentially harmful silicone/latex catheters and may be involved in the pathophysiology of catheter-induced urethral strictures. *In vitro* biocompatibility tests may be performed at both 20 and 37°C. Glass test tubes may be used for *in vitro* complement but not for kallikrein-kinin investigations.

Several authors have reported urethral strictures in connection with the use of indwelling urinary catheters (Ruutu *et al.*, 1982; Sutherland *et al.*, 1982; Wesley-James, 1982). The strictures differ from the usual post-catheterisation strictures in both location and extent and have been particularly observed with catheters containing latex (Ruutu *et al.*, 1982). The stricture formation is believed to occur when poor blood flow allows toxic material released from the catheters to accumulate in the surrounding tissue (Wilksch *et al.*, 1983; Elhilali *et al.*, 1986). Tissue toxicity studies and *in vitro* cytotoxicity studies have demonstrated a low biocompatibility of some urinary catheters containing latex (Ruutu *et al.*, 1985; Talja *et al.*, 1985; Våge *et al.*, 1990). In animal studies with reduced local urethral blood perfusion, infiltration of inflammatory polymorphonuclear cells occurred when toxic catheters were implanted in the urethra, in contrast to the lack of tissue response when all-silicone catheters were implanted (Talja *et al.*, 1986).

In plasma, 4 protein systems exist in which the components undergo sequential proenzyme-enzyme reactions. These are the complement, the kallikrein-kinin, the fibrinolytic and the coagulation systems. They have the capacity to act in concert and partially cross-activate one another (Sundsmo and Fair, 1983). They generally participate in the defence of the host and in maintenance of homeostasis. They also play a role in the pathogenesis of inflammatory tissue injury. Components of these systems are known to interact with receptors, leading to stimulation of various cell functions (Saito, 1980).

It has been shown that latex-containing urinary catheters could activate the complement system and were possibly implicated in catheter-induced urethral inflammation (Garred *et al.*, 1989). The purpose of the present study was to investigate whether urinary catheters were capable of activating the other cascade systems. We also wished to

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investigate the effect of time and temperature in these systems in order to give general guidelines for biocompatibility studies. The experiments were performed in both glass and plastic tubes in order to determine the most suitable test tubes for such experiments.

## Materials and Methods

### *Preparation of samples*

The cascade system source was obtained from blood samples from 12 healthy members of staff (6 females and 6 males) with a median age of 35 years. Half of the blood samples from each individual was collected in glass tubes and the other half in plastic tubes, both containing the anticoagulant natrium-citrate (0.1 M) and centrifuged after 30 min. The citrate plasma fractions were pooled and kept at 4°C until the start of the experiments.

Two brands of urinary catheter were investigated: one non-coated combined silicone/latex catheter, with latex being the main component and one all-silicone catheter, identical to those used by Garred *et al.* (1989). All catheters were delivered sterile and handled under clean conditions. Fifteen catheters from each brand were cut in pieces approximately 24 mm$^2$ in surface-area.

The investigation was divided into 2 groups, 1 using plastic and the other using glass tubes, with a total of 60 tubes in each group. In both groups there were 2 subgroups in which experiments were performed at 20 and 37°C, respectively. For the combined silicone/latex catheters the test tubes (5 ml) were prepared as follows; 40 test tubes (20 glass and 20 plastic) were filled to the top with catheter pieces and 2.5 ml plasma were then added. In the same way 40 test tubes were filled with all-silicone catheter pieces; 40 tubes containing plasma only served as controls.

The first sample was drawn after 15 minutes' incubation and the rest at 1, 2, 4 and 9 h. Six test tubes were obtained from each subgroup. 1 ml was drawn from each glass tube and put into cryotubes (TecNunc, Roskilde, Denmark); 300 µl were drawn from each plastic tube and put into sample cups (Cobas Bio, Hoffman La Roche, Basel, Switzerland). The remaining test tubes were shaken every hour. The plasma samples were immediately frozen at −70°C to avoid further activation and stored at this temperature until assayed *en bloc*.

### *Analyses of complement activation products*

Complement activation was assessed in an enzyme immunoassay (EIA) specific for an epitope in C3 activation products not expressed in native C3 (Garred *et al.*, 1988). In brief, polystyrene plates were coated with a mouse monoclonal antibody (bH6) specific for a C3 neoepitope expressed on C3b, iC3b and C3c, but not on native C3. A rabbit anti-human C3c antiserum (Behring, Marburg, FRG) was used in the second antibody layer. Finally, a peroxidase conjugated anti-rabbit Ig was added (Amersham International, UK). The substrate was 2, 2′-azino-di-(3-ethylbenzthiazoline sulphonic acid) (ABTS). The results were read on a Dynatech MR 580 plate reader (Alexandria, Virginia, USA) against a standard of zymosan-activated serum defined as containing 1000 arbitrary units/ml (AU/ml). The results were analysed by an Apple II computer with a Dynatech Immunosoft program.

### *Analyses of the kallikrein-kinin, fibrinolysis and coagulation systems*

Chromogenic peptide substrate assays were used to determine plasma kallikrein activity (KK), prekallikrein (PKK), functional plasma kallikrein inhibition (KKI), prothrombin (Pthr), antithrombin III (AT III), plasmin (PL), plasminogen (Plg) and functional antiplasmin activity (AP). The assays were performed on an automated centrifugal analyser (Cobas Bio, Hoffman La Roche, Basel, Switzerland) as previously described (Aasen *et al.*, 1982). All proenzymes and functional inhibition values were expressed as a percentage of normal plasma pool values. Enzyme activities were expressed as units/litre (U/L).

The complement experiments were performed twice with 2 parallels each time. The results are the median of 4 parallels. The kallikrein-kinin, fibrinolytic and coagulation experiments were performed in 2 parallel arrangements. The results indicate the mean of 2 different experiments.

## Results

### *Complement system*

*Complement activation at 20°C* (Fig. 1). When the silicone/latex catheters were incubated in plasma, the value for C3 activation products increased from 33 AU/ml (citrate plasma control) to 47 AU/ml after 15 min. After 1 and 2 hours' incubation an increase to 69 and 85 AU/ml respectively was observed. This increase continued at 4 h (141 AU/ml) and reached a maximum at 9 h (279 AU/ml).

When the all-silicone catheters were incubated in plasma, no increase for C3 activation products

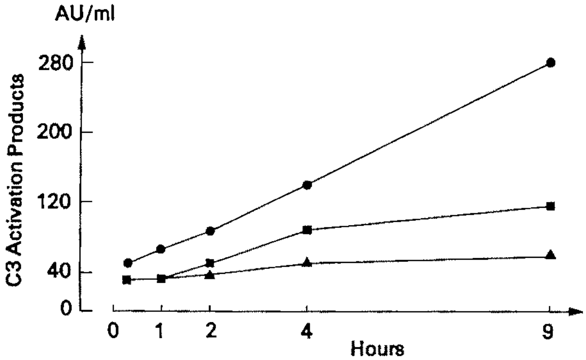

**Fig. 1** Complement activation (C3 activation products) in citrate plasma at 20°C. Circles indicate activity in the presence of silicone/latex catheters. Squares indicate activity in the presence of all-silicone catheters. Triangles indicate activity without the presence of catheters.

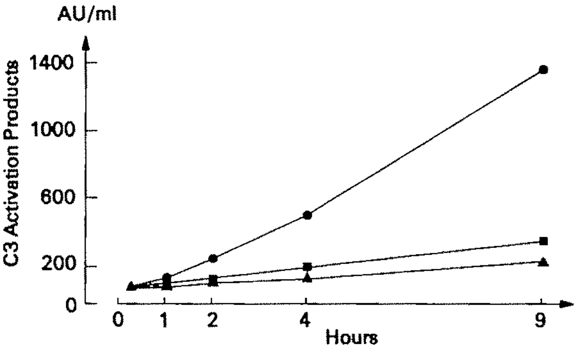

**Fig. 2** Complement activation (C3 activation products) in citrate plasma at 37°C. Circles indicate activity in the presence of silicone/latex catheters. Squares indicate activity in the presence of all-silicone catheters. Triangles indicate activity without the presence of catheters.

was observed from the citrate plasma control (33 AU/ml) after 15 min and 1 h. After 2 hours' incubation a minor increase was found (52 AU/ml). This increase continued at 4 h (91 AU/ml) and reached a maximum at 9 h (115 AU/ml).

In the citrate plasma control the baseline value was 33 AU/ml. After 9 h a maximum of 56 AU/ml was reached.

*Complement activation at 37°C* (Fig. 2). When the silicone/latex catheters were incubated in plasma the value observed for C3 activation products increased from 33 AU/ml (citrate plasma control) to 52 AU/ml after 15 min. After 1 and 2 hours' incubation an increase to 104 and 212 AU/ml respectively was observed. This increase continued at 4 h (488 AU/ml) and reached a maximum at 9 h (1324 AU/ml).

When the all-silicone catheters were incubated in plasma, no increase for C3 activation products was observed from the citrate plasma control (33 AU/ml) after 15 min. The value reached 71 AU/ml at 1 h. After 2 hours' of incubation an increase to 104 AU/ml was found. This increase continued at 4 h (168 AU/ml) and reached a maximum at 9 h (329 AU/ml).

In the citrate plasma control the baseline value was 33 AU/ml. After 9 h a maximum of 194 AU/ml was reached.

No difference in C3 activation was found between samples incubated in glass or plastic tubes.

As shown above, a marked difference in absolute C3 activation was observed between 20 and 37°C. However, no relative amplification occurred between 20 and 37°C, since the ratio between test samples and controls remained constant (Table).

*Kallikrein system*

*Plasma kallikrein (KK) activity in plastic test tubes* (Fig. 3). The baseline value for KK activity was 24 U/L when plasma without catheters was incubated in the plastic test tubes. This level was maintained during the test period. When the silicone/latex catheters were tested, a marked increase was seen in KK activity after 15 min (35 U/L). This level was maintained during the test period. When the all-silicone catheters were tested, no increase was seen after 15 min compared with the baseline value and the level was maintained during the test period. Virtually identical results were obtained at 20 and 37°C.

*Plasma kallikrein (KK) activity in glass test tubes.* The baseline value for KK activity was 44 U/L when plasma without catheters was incubated in the glass test tubes. When the silicone/latex catheters were tested, a marked increase was seen in KK activity after 15 min (75 U/L). This level was maintained during the test period. When the all-silicone catheters were tested, no increase was seen after 15 min compared with the baseline value. This level was maintained during the test period. Virtually identical results were obtained at 20 and 37°C.

**Table** Relative Complement Activation at 20 and 37°C

| | |
|---|---|
| 20°C | |
| All-silicone at 9 h/control at 9 h | 115/56 = 2.0 |
| Silicone/latex at 9 h/control at 9 h | 279/56 = 5.0 |
| 37°C | |
| All-silicone at 9 h/control at 9 h | 329/194 = 1.7 |
| Silicone/latex at 9 h/control at 9 h | 1324/194 = 6.8 |

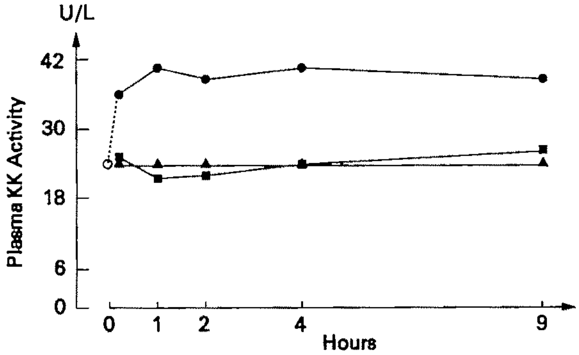

**Fig. 3** Plasma kallikrein (KK) activity in citrate plasma at 20°C. Circles indicate activity in the presence of silicone/latex catheters. Squares indicate activity in the presence of all-silicone catheters. Triangles indicate activity without the presence of catheters. Open circle indicates baseline value before incubation.

*Kallikrein inhibition (KKI)*. The baseline value for KKI activity was 106% when plasma without catheters was incubated in the plastic test tubes. This level was maintained during the test period. When the silicone/latex catheters were tested, a slight decrease was seen in KKI activity after 15 min (103%). After 1 h the level decreased to 96%. This level was maintained during the test period. When the all-silicone catheters were tested, no change was seen after 15 min compared with baseline values. This level was maintained during the test period. Virtually identical results were obtained at 20 and 37°C.

In glass test tubes the KKI results were similar to those obtained in plastic tubes but the values were found to be approximately 40% lower in all samples tested.

*Prekallikrein (PKK)*. No changes in prekallikrein (PKK) values were found either in control plasma or in plasma incubated with silicone/latex catheters or all-silicone catheters. This was valid both for glass and plastic tubes at both temperatures.

### *Coagulation system and fibrinolytic system*

No activation was induced by the silicone/latex or the all-silicone catheters either in the coagulation system (Pthr and AT III) or in the fibrinolytic system (PL, Plg and AP).

## Discussion

This study has shown that silicone/latex catheters activated the kallikrein-kinin system within the first 15 min of the test period. A pronounced, long-lasting time- and temperature-dependent activation of the complement system was observed. When all-silicone catheters were tested, only minimal changes were observed in both systems.

Prekallikrein is converted to enzymatically active kallikrein when exposed to a negatively charged surface. Kallikrein releases bradykinin by proteolytic cleavage from high molecular weight-(HMW)-kinogen. Bradykinin increases vascular permeability, diminished arterial resistance and induces hypotension, vascular margination and migration of leukocytes into tissues (Cooper and Cochrane, 1983). The activation of complement enhances membrane permeability and activation of polymorphonuclear inflammatory cells (Jacobs *et al.*, 1980).

Our study has shown that a rise in temperature from 20 to 37°C influenced complement activation independent of the activating agent. Similar results have been obtained previously (Mollnes *et al.*, 1988). When the catheters were tested, a marked difference in absolute complement activation was observed between 20 and 37°C, but almost no relative amplification occurred (Table). This indicates that although temperature is important, when absolute data are compared it is not critical when the degree of catheter-induced activation is compared with the controls. In the contact system no difference in the activation pattern was seen between 20 and 37°C.

Prekallikrein interacts on negatively charged surfaces such as glass, leading to activation of the contact system (Cooper and Cochrane, 1983). Consumption of plasma protease inhibitors such as C1 inhibitor (C1INH) may lead to autoactivation of prekallikrein since C1INH inhibits not only C1 but also prekallikrein (Saito, 1980). In the present study we demonstrated that the combined silicone/latex catheter activated the kallikrein-kinin system. No such activation was observed when all-silicone catheters were tested, which is consistent with the fact that positively charged surfaces do not activate the contact system (Nossel *et al.*, 1968). Activation of the kallikrein-kinin system reached a plateau after 15 min, in contrast to the activation of complement, which continued during the whole test period of 9 h. The activation mechanisms may thus differ in these systems. It has been shown that both latex catheter membranes and soluble factors from the catheters activated complement (Våge *et al.*, 1990). Probably the activation of the contact system depends largely on the interaction between prekallikrein and the surface, which may be either rapidly saturated or downregulated, leading to ceased activation.

Our data indicate that both complement activation products and bradykinin are generated by potentially harmful silicone/latex catheters and may be involved in the pathophysiology of catheter-induced urethral strictures. The new generation of sensitive complement activation assays has proved very useful for biocompatibility testing. Temperature does not seem to influence the relative results and the incubation experiments can be performed in either glass or plastic tubes. Kallikrein-kinin investigations, which must be performed in plastic tubes, may give valuable additional information when the biocompatibility of artificial surfaces is studied.

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# Haemospermia: a Prospective Study

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Summary—A prospective study of 74 men with haemospermia is presented. Most (76%) had experienced 1 or 2 episodes only and 9 (12%) were over 40 years old. Simple investigations led to a diagnosis in all 9 of these men and of those under 40, no pathology could be detected in 48%. A diagnosis was made in 32 of the remaining 34 men by simple investigations. In patients over 40 years of age with haemospermia, a potentially treatable cause will normally be found by routine investigation which should include cystoscopy. In younger men, non-invasive investigation alone should identify any pathology. Invasive investigations should be reserved for those patients in whom the problem is prolonged, excessive or in association with other symptoms.

Haemospermia is a common and worrying symptom which frightens some men into seeking early medical advice whilst others may suffer fear, anxiety or embarrassment and delay reporting to a doctor for months or years (Ross, 1969).

The symptom has been recognised for hundreds of years and has been attributed to many and varied causes, including seminal vesiculitis, tuberculosis, unbridled licence short of physical indulgence, "haemorrhage *ex vacuo*", the male menopause, constipation, blood dyscrasias, bilharzia and hypertension. The presence of a direct communication between the venous system and seminal vesicle has been implicated (Magid and Hejtmancik, 1957) and other causes such as enlarged posterior urethral veins, utricular cysts, heterotrophic calcification and serious underlying systemic diseases have been suggested (Cattolica, 1982; Marshall and Fuller, 1983; Van Poppel *et al.*, 1983; Sinokrot and Pryor, 1987). There have, however, been few studies on large numbers of men with haemospermia and they differ in their recommendations as to how the symptom should be investigated and its significance. Ross (1969) retrospectively reviewed 31 patients and suggested that many fell into an idiopathic or essential group with no cause being found. Another retrospective review of 150 patients from the Mayo Clinic (Leary and Aguilo, 1974), with a follow-up of 5 to 23 years, concluded that patients with haemospermia did not develop long-term problems and that investigation should be by examination and urine analysis only. Yu *et al.* (1977) retrospectively reviewed 65 patients in Hong Kong. Although renal tuberculosis was a common finding, they felt there was no specific aetiology for the haemospermia and that full investigation was unnecessary. Fletcher *et al.* (1981) reviewed 81 patients who had undergone a variety of investigations and found an explanation for haemospermia in 86%. They found infection to be the most common cause in men under 30 years of age and recommended that all patients should have culture of urine, semen and prostatic fluid, proceeding to cystoscopy and vasography if these investigations proved negative. Payne *et al.* (1985), in a large series of patients undergoing vasography, identified 26 patients with haemospermia, 73% of whom had abnormal vasograms. It was suggested that vasography was a useful investigation in recalcitrant haemospermia. In addition, magnetic resonance imaging was shown to be of value in a patient with chronic haemospermia due to a Mullerian duct cyst (Neustein *et al.*, 1989).

In view of the paucity of prospective studies of

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this condition and the confusion as to its aetiology and mode of investigation, a prospective study of men presenting with haemospermia was initiated.

## Patients and Methods

All patients presenting with haemospermia during a 6-year period (1984–1989) were studied prospectively according to a standard investigation protocol. After history and physical examination, including digital rectal assessment of the prostate, mid-stream urine and semen specimens were sent for microscopy and culture. A plain abdominal X-ray was taken and cystoscopy performed under general anaesthesia. More recently, flexible cystoscopy as an out-patient procedure under local anaesthesia has been used. Other investigations were performed as indicated by any positive findings and treatment instituted when necessary. Patients were reviewed routinely after 3 months and at other times if their condition warranted.

## Results

Of the 74 men studied, 56 (76%) had experienced only 1 or 2 episodes of haemospermia. The age range was 20 to 73 years (mean 29.6), with 9 patients (12%) aged over 40. The length of history varied from 3 weeks to 7 months. The patients were divided into 2 groups: Group 1 (n = 65) less than 40 years old and Group 2 (n = 9) 40 years and older. Of the 65 patients in Group 1, no abnormalities were found in 31. The results of investigations in the remaining 34 and the eventual outcome are shown in the Table. Of the 31 patients in whom no cause could be found, 8 continued to have haemospermia when seen at their 3-monthly review, but in none was the bleeding profuse or associated with other symptoms. These patients were reassured that no serious cause for the haemospermia could be found and further follow-up was offered on request. Of the 9 patients in Group 2, 4 were aged between 41 and 60 years, 4 were 61 to 70 years and 1 was 73 years old. A diagnosis or finding to account for the haemospermia was achieved in all 9 patients. Significant and symptomatic benign prostatic hypertrophy was found in 5 men; in 3 cases cystoscopy showed large, tortuous and friable veins in the prostatic urethra and bladder neck. Hypertension was present in 3 men, all of whom were under treatment. A transurethral resection of the prostate (TURP) had been performed 9 months previously in 1 patient and he also complained of haematuria. Cystoscopy showed florid granulation tissue in the prostatic fossa and this was treated with further resection. Numerous prostatic calculi were seen on plain X-ray in 1 patient and obviously apparent on cystoscopy. The youngest patient in this group (age 43 years) had occasional dysuria and pain on ejaculation and a tender prostate, with pus cells seen on microscopy of seminal fluid. He was treated with antibiotics to good effect. One patient had calcified seminal vesicles also noted on plain X-ray, but early morning urine specimens were negative and no ova or cysts were seen on urine microscopy. The oldest patient in this group (73 years) complained of a "wet dream" with bloodstained semen. He had an obvious prostatic carcinoma on rectal examination and subsequently underwent TURP and hormonal therapy.

**Table** Findings and Follow-up in Patients <40 Years (Group 1, n = 65)

| *Findings (no.)* | *Comments* | *Follow-up at 3 months* |
|---|---|---|
| No abnormality (31) | — | Resolved (23)<br>Remainder under review |
| Prostatitis (21) | Positive semen culture (6)<br>Pus cells seen (13) | All resolved |
| Urethritis (5) | Recent non-specific urethritis | All resolved |
| Urinary tract infection (1) | Unexplained aetiology | No recurrence |
| Urethral stricture (1) | Previous STD | Flow rate satisfactory<br>Follow-up continues |
| Self-instrumentation (1) | Sexual foreplay | No recurrence |
| Posterior urethral vein (1) | Bleeding + on urethroscopy, vein diathermised | No recurrence |
| Sexual excess (1) | Intercourse × 8/24 h | No recurrence |
| Meatal papillomata (1) | Treated with cautery | No recurrence<br>Required 2 treatments |
| Urethral condylomata (1) | Treated with diathermy | No recurrence |
| Prostatic calculi (1) | Unexplained aetiology | Mild haemospermia × 2 |

## Discussion

This study has confirmed that haemospermia in young men is an entirely benign condition which does not warrant extensive investigation. Conversely, in older men, the presence of haemospermia is often associated with other symptoms and appears to indicate that significant pathology is present. In these patients, however, a history, examination and investigation by simple means is normally sufficient to achieve a diagnosis. In none of the men studied was the symptom associated with severe or debilitating disease of other organ systems. Such a situation would normally be apparent and it is hard to believe that haemospermia may be the sole presenting symptom, as has been suggested (Marshall and Fuller, 1983).

Of the young men studied, many had symptoms of relatively short duration and 31 (41%) were classed as idiopathic or essential (Ross, 1969). These findings were at variance with those of Fletcher *et al.* (1981), who achieved a diagnosis in 86% of their patients, but only 8 patients in this idiopathic group continued to have haemospermia at the 3-monthly follow-up, confirming the benign and self-limiting nature of the condition (Leary and Aguilo, 1974). It would be difficult to justify an invasive investigation such as vasography in these men unless the bleeding became severe or other symptoms were present. Inflammatory causes are obviously common, although the incidence in this study was not as high as has been reported (Fletcher *et al.*, 1981). These patients are normally identified easily and can be effectively treated.

It is difficult to explain why sexual excess could be the cause of haemospermia unless another precipitating cause was present. There was certainly no indication, in the patient described, that he had stopped short of "physical indulgence", having achieved a commendable 8 ejaculations within a 24-h period (Parker, 1942).

The presence of enlarged urethral veins as a cause of haemospermia may be more significant than is appreciated, as it has been suggested that the veins only become engorged during or immediately after erection (Cattolica, 1982) and thus would not be apparent on routine cystoscopy.

In the older age group, hypertension is common and although it is difficult to say whether this may contribute to haemospermia, it would appear to be an unlikely aetiological factor. Similarly, benign prostatic enlargement is an almost normal finding and only a small proportion of such patients complain of haemospermia. Certainly the presence of large tortuous veins in the prostatic fossa or bladder neck provides an attractive cause for otherwise unexplained haemospermia, especially when the passage of a cystoscope causes obvious bleeding in the prostatic urethra.

Many patients will have other symptoms in addition to haemospermia revealed on direct questioning and these may require further investigation, especially if haematuria is present. Although a somewhat simplistic conclusion, we agree with Tolley and Castro (1975) that the presence of other symptoms warrants investigation.

In conclusion, most men under 40 years of age who present with haemospermia will have an inflammatory cause or fall into the essential group. Simple investigations alone should identify pathology and very few patients will require extensive or invasive investigations. In patients over 40, other symptoms will often be present and pathology will normally be found. Investigation should be pursued until a diagnosis is reached and should include cystoscopy at the very least.

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# Vasal Injuries during Childhood and their Effect on Subsequent Fertility

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Summary—Thirty subfertile males had testicular obstruction following inguinal or pelvic surgery in childhood. All 13 patients with bilateral obstruction were azoospermic and 6 had developed antibodies to spermatozoa. Of 17 patients with unilateral obstruction, 11 had oligozoospermia and 6 had normal sperm counts: all had high titres of antibodies to spermatozoa (a significant difference from the men with bilateral obstruction). This indicates that male infertility can result from vasal or epididymal injuries in childhood due either to the obstruction itself or its immunological consequences.

Following corrective surgery and prednisolone treatment for the antibodies, where appropriate, 5/17 patients with unilateral blocks and 1/11 with bilateral blocks successfully produced pregnancies.

Injuries to the vasa deferentia may occur during surgery of the inguinal region or pelvis in male infants and children. These are not always recognised intra-operatively and, in addition, even if the vasa are carefully preserved, damage to their blood supply can result in fibrosis and subsequent obstruction.

Bilateral injury obviously causes sterility. Unilateral testicular obstruction may also lead to infertility due to the presence of antibodies to spermatozoa, and this has been demonstrated both experimentally (Rumke and Titus, 1970; Kessler *et al.*, 1985) and clinically (Hendry, 1986). Obstruction leads to diversion of spermatozoa to testicular lymphatics (Ball *et al.*, 1982; Ball and Setchell, 1983) and this breach of the blood-testis barrier (Johnson, 1973) produces an antigenic challenge. The resulting appearance of antibodies in the circulation and in the seminal plasma is responsible for agglutination and immobilisation of spermatozoa emerging from the contralateral non-obstructed testis, and thus fertility may be impaired.

There is some evidence that experimental injury to the vas deferens before puberty in rats is associated with later production of antibodies to spermatozoa and that early vasal reconstruction prevents this phenomenon (Pederson *et al.*, 1987). However, there have been no detailed studies in humans to ascertain whether vasal injuries in childhood are of relevance to later fertility.

## Patients and Methods

Thirty men aged 20 to 41 years presenting with infertility were studied. All had undergone surgery or trauma before the age of 12 years and this was demonstrated by surgical exploration to have resulted in injury to the vas deferens or epididymis. Twenty patients had undergone correction of hydroceles or congenital hernias, 1 combined with contralateral orchiopexy; 3 had had orchiopexies only (1 unilateral and 2 bilateral), 4 had undergone rectal surgery for imperforate anus (3) or Hirschsprung's disease (1), 1 had undergone multiple bilateral ureteric reimplants, 1 had vasal damage due to an intra-abdominal drain following laparotomy in infancy, 1 had undergone cystoprostatectomy for rhabdomyosarcoma, and 1 had sustained a ruptured urethra (Tables 1 and 2).

All patients had semen analysis, and antibodies to spermatozoa were measured in seminal plasma and serum by the tray agglutination test (TAT)

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**Table 1** Details of 17 Patients with Unilateral Testicular Obstruction

| | | | *Before treatment* | | | *After treatment* | | |
|---|---|---|---|---|---|---|---|---|
| *Patient no.* | *Original pathology* | *Age (years)* | *Sperm count (M/ml)* | *Serum TAT* | *Treatment* | *Sperm count (M/ml)* | *Serum TAT* | *Pregnancy* |
| 1 | Right IH<br>urethral injury | <1<br>6 | 1 | 256 | V-v | 1 | N/A | |
| 2 | Right IH | <1 | 46 | 512 | V-v+P | 57 | 4 | Yes |
| 3 | Right IH<br>Left UDT | <1<br><1 | 1 | 64 | T-v-v | 8 | 32 | Yes |
| 4 | Right IH | <1 | 2 | 32 | T-v-v | 12 | 16 | |
| 5 | Right IH | 4 | 1 | 16 | T-v-v | 44 | 0 | |
| 6 | Laparotomy+drain through vas | <1 | 1 | 512 | T-v-v | 14 | 0 | Yes |
| 7 | Right IH | 7 | 20 | 64 | Orch | 22 | 2048 (seminal plasma 0) | Yes |
| 8 | Left IH | 4 | 71 | 32 | Orch | 165 | 16 | |
| 9 | Left IH | 12 | 25 | 1024 | Orch | 28 | 256 | |
| 10 | Left UR × 2<br>Right UR × 1 | 12<br>27 | 1 | 1024 | Orch+P | 14 | 64 | Yes |
| 11 | Hirschsprung's disease | 2 | 89 | 1024 | Orch+P | 24 | 64 | |
| 12 | Right IH | <1 | 7 | 1024 | Orch+P | 35 | 32 | |
| 13 | Right IH | <1 | 1 | 128 | Orch+P | 7 | 64 | |
| 14 | Bilateral IH (unilateral block) | <1 | 35 | 1024 | Orch+P | 40 | 0 | |
| 15 | Left IH | 4 | 25 | 256 | P+orch | 21 | 1024 | |
| 16 | Right IH | 8 | 9 | 256 | P | N/A | N/A | |
| 17 | Ruptured urethra | 9 | 17 | 128 | P | 70 | 32 | |

IH: inguinal hernia or hydrocele
UDT: undescended testis
UR: ureteric reimplant
V-v: vasovasostomy
P: prednisolone
T-v-v: trans-vasovasostomy
Orch: orchiectomy
N/A: not available

(Friberg, 1974). A serum hormone profile was done prior to scrotal exploration and all patients had normal FSH concentrations.

The scrotum was explored under general anaesthesia through a midline incision (Hendry *et al.*, 1983) and testicular biopsies were taken. If inspection of the epididymes with magnification (×2) revealed dilated tubules (Fig. 1), the vas was opened by a short linear incision and vasography done using a 2 F Portex cannula. The colour and consistency of any fluid within the vas were noted.

Once the level of the block was defined, the groin was explored in suitable cases through a separate counter-incision to expose the inguinal part of the vas (Fig. 2). Reconstruction was done whenever possible by side-to-side vasovasostomy using 6/0 prolene with ×2 magnification (see below for details). Prednisolone treatment for antibodies to spermatozoa was given when indicated (Hendry *et al.*, 1990).

## Results

### *Semen analysis and TAT*

The 17 patients with unilateral testicular obstruc-

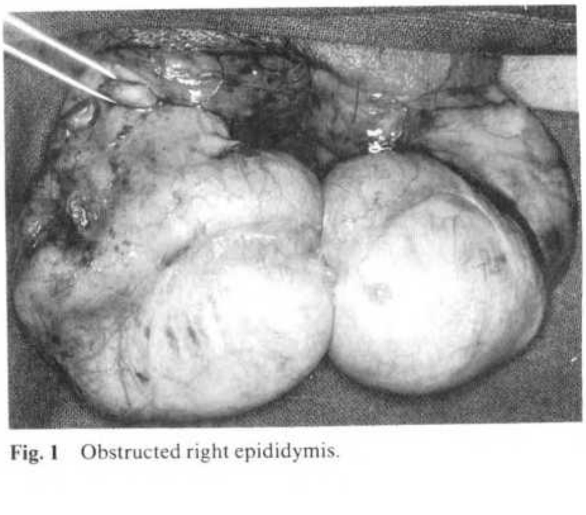

**Fig. 1** Obstructed right epididymis.

**Table 2** Details of 13 Patients with Bilateral Testicular Obstruction

| | | | *Before treatment* | | | *After treatment* | | |
|---|---|---|---|---|---|---|---|---|
| *Patient no.* | *Original pathology* | *Age (years)* | *Sperm count (M/ml)* | *Serum TAT* | *Treatment* | *Sperm count (M/ml)* | *Serum TAT* | *Pregnancy* |
| 18 | Bilateral IH | 7 | 0 | 16 | V-v | N/A | N/A | |
| 19 | Right IH<br>Left torsion | 5<br>11 | 0 | 0 | V-v | 11 | 0 | Yes |
| 20 | Imperforate anus | <1 | 0 | 128 | E-v+t-v-v | 0 | N/A | |
| 21 | Right IH | 3 | 0 | 256 | E-v+t-v-v | 0 | N/A | |
| 22 | Right IH<br>Gonorrhoea | 2<br>28 | 0 | 0 | E-v+t-v-v | 0 | N/A | |
| 23 | Bilateral IH | 7 | 0 | 16 | T-v-v | 0 | N/A | |
| 24 | Urethral valves<br>Left IH × 1<br>Right IH × 3 | <1<br><1<br><1 | 0 | 0 | Sperm res | ++ | N/A | |
| 25 | Cystoprostatectomy for rhabdomyosarcoma | 3 | 0 | 0 | Sperm res | 0 | N/A | |
| 26 | Imperforate anus | <1 | 0 | 0 | Sperm res | ++ | N/A | |
| 27 | Imperforate anus | <1 | 0 | 0 | Inoperable | N/A | N/A | |
| 28 | Bilateral UDT | 8 | 0 | 16 | Inoperable | N/A | N/A | |
| 29 | Bilateral UDT | 8 | 0 | 0 | Inoperable | N/A | N/A | |
| 30 | Bilateral IH | <1 | 0 | 64 | Inoperable | N/A | N/A | |

IH: inguinal hernia or hydrocele
UDT: undescended testis
V-v: vasovasostomy
T-v-v: trans-vasovasostomy
E-v: epididymovasostomy
Sperm res: sperm reservoirs
N/A: not available

tion had sperm counts ranging from 1 to $89 \times 10^6$/ml, with 11 having counts below $20 \times 10^6$/ml. All had serum antibodies to spermatozoa, with titres >1:128 in 12 cases (70%). The 13 patients with bilateral testicular obstruction all had azoospermia, but only 6 (46%) had serum antibodies and none of the 6 had antibody titres >1:128. Antibody titres of the patients with bilateral obstruction were compared with the antibody titres of patients with unilateral obstruction (Fig. 3) and the difference between the 2 groups was significant at the 1% level (Wilcoxon's rank sum test).

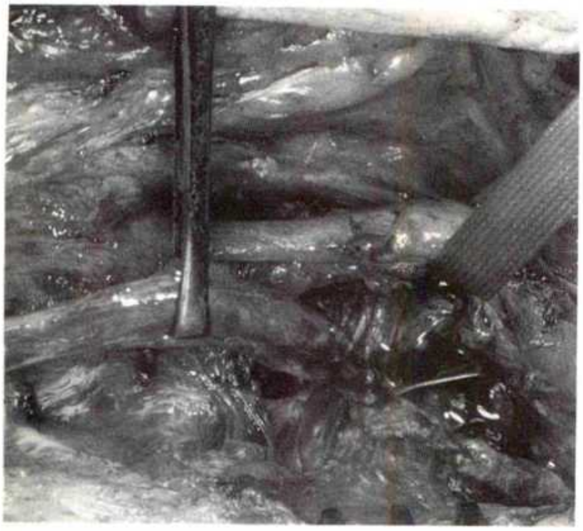

**Fig. 2** Vasal block in inguinal canal.

### *Operative findings and outcome for 17 patients with unilateral obstruction*

Reconstructive surgery was carried out in 6 cases after an absent or fibrosed vas was found at or below the inguinal canal on scrotal exploration (Table 1); 4 patients had transvasovasostomies and 2 had vasovasostomies. Post-operative sperm counts were improved in all but 1 case (Patient no. 1).

Two patients successfully fathered children after transvasovasostomy alone and 1 was successful after vasovasostomy and post-operative prednisolone.

Eleven patients were found to have a vasal block above the internal ring (5 cases) or absence of the greater part of the vas (6), which made repair impossible. In 9 cases orchiectomy and insertion of a testicular prosthesis was carried out as a secondary operation after full discussion with the patient and

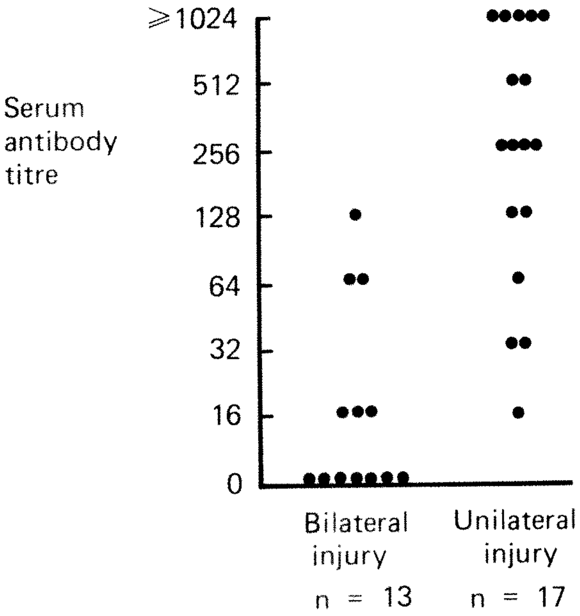

**Fig. 3** Serum antibody titres in men with unilateral and bilateral vasal blocks.

his partner. Three patients had orchiectomy alone, 5 had orchiectomy with post-operative prednisolone and 1 had prednisolone followed by orchiectomy; 2 patients declined orchiectomy and were treated with prednisolone only.

After orchiectomy alone, 2 patients (Nos. 8 and 9) had an increase in sperm count and a decrease in serum antibody titre, but failed to impregnate their partners; the other patient (7) had no change in sperm count, but his seminal plasma antibody titre became negative and his wife became pregnant. All 6 patients who had orchiectomy and steroids had either an increase in sperm count or a decrease in antibody titre or a combination of both. One patient who had steroids only had an increase in sperm count and a decrease in antibody titre (Table 1).

### *Outcome for 13 azoospermic patients*

Reconstructive surgery was carried out in 6 azoospermic patients, 3 were treated with sperm reservoirs (Brindley *et al.*, 1989) and 4 were considered to be inoperable (Table 2). Although sperm counts were identified in 3 cases, only 1 patient has successfully impregnated his partner.

## Discussion

This study confirms the vulnerability of the vas deferens during groin surgery in infancy and childhood. Although most of the injuries occurred as a result of dissection of the patent processus vaginalis during correction of hydrocele or congenital hernia, the conclusions can be adduced to the arguments for and against early orchiopexy for testicular maldescent. Impaired fertility is common in association with unilateral and bilateral cryptorchidism (Kogan, 1987) but the optimum age for orchiopexy remains controversial. The presumed benefits of early placement of the testis in the scrotum must be considered in the context of a higher incidence of vasal and epididymal injuries when operating in infancy, even in experienced hands (Sparkman, 1962). It has been shown experimentally that histological damage to the vas deferens may occur through handling (Shandling and Janik, 1981; Janik and Shandling, 1982) and it is therefore possible that vasal obstruction may occur as a consequence of hernial sac dissection even when the vas has not been completely transected. If both vasa are blocked, infertility is inevitable and the reasons are obvious. However, if only 1 vas is blocked the changes are more subtle and may well be missed. Comparison of the 2 groups (Fig. 3) indicates that the causes of the infertility are different, being presumably obstructive in the azoospermic group but due to secondary immunological changes in the unilaterally obstructed group. It is known that the formation of antibodies to spermatozoa is less common with congenital obstructions than with acquired postpubertal blocks (Hendry *et al.*, 1983; Patrizio *et al.*, 1989). It is likely, therefore, that there is a considerable number of men with unilateral blocks acquired in childhood who have not developed antibodies and who are fertile (Kumar *et al.*, 1989). The incidence of this complication is probably substantially higher than previously suspected, leading to infertility only when damage is bilateral or associated with high antibody titres.

Assessment of the subfertile male should always include questioning about groin surgery or testicular maldescent in childhood. On examination the changes in the obstructed epididymis may be difficult to detect, but there is often some fullness of the tail and the groin scar is visible on close inspection. The presence of serum antibodies, particularly producing head-to-head agglutination of spermatozoa, should also arouse suspicion of unilateral obstruction (Hendry *et al.*, 1982). Confirmation of the diagnosis requires surgical exploration through a midline scrotal incision, which provides an opportunity for bilateral inspection of the epididymes with vasography and testicular biopsies. If the presence of obstruction is confirmed, definitive repair can be done through an appropriate counter-incision. If repair is impossible and the antibody levels are high, orchiectomy with insertion of a prosthesis can be carried out at a later operation once the situation has been discussed fully with the patient and his female partner.

The mechanism of infertility in patients with cryptorchidism may be related to failure of germ cell maturation (Huff *et al.*, 1989) or even to congenital epididymal and vasal defects (Gill *et al.*, 1989). We have shown that iatrogenic injuries to the vas deferens or epididymis in childhood can also result in infertility by reducing sperm output and by stimulating antibody production in certain individuals who are immunologically responsive. In patients with unilateral testicular obstruction, fertility may be improved by a combination of surgical and medical management and removal of the obstructed testis should always be considered as a method of reducing the antigenic burden. Patients with bilateral obstruction have a poor prognosis and the underlying cause of infertility does not appear to be primarily immunological. It is possible that the antigenic stimulus is small in cases of bilateral obstruction as a consequence of reduced spermatogenesis associated with failure of germ cell maturation (Friberg and Kjessler, 1975).

There is some evidence that early treatment with buserelin may cause an increased germ cell count in the undescended testis (Hadziselimovic *et al.*, 1987). Clearly, further research into non-operative methods of management of the undescended testis is desirable if iatrogenic injuries are to be avoided. When surgery is necessary, meticulous attention to detail and the use of magnification and bipolar diathermy should help to minimise trauma to the vas deferens and its blood supply. In the meantime it is important to be aware that some of these patients can be helped by identifying and treating antibodies to spermatozoa.

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PAEDIATRIC UROLOGY

# Outcome of Antenatally Diagnosed Pelviureteric Junction Hydronephrosis

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Summary—Over a 6-year period, in a series of 107 consecutive patients with antenatally detected urological anomalies, 45 had pelviureteric junction (PUJ) hydronephrosis (66 units). Of these, 24 units (36%) had obstructive (group I) and 42 (64%) non-obstructive hydronephrosis (group II). Significantly compromised renal function was found only in group I. Treatment in group I was by an early pyeloplasty; in group II the patients were kept under close review. During the 6-year period, 2 units (5%) in group II, deteriorated, 13 (31%) improved and 27 (64%) were unchanged.

These results suggest that early in life, antenatally diagnosed PUJ hydronephrosis without obstruction may be a relatively benign condition but will require long-term follow-up in order to determine the natural history of the condition.

In recent years, clinicians have been confronted with an increasing number of neonates presenting with antenatally detected upper urinary tract dilatation in whom the underlying pathology and significance are difficult to interpret.

Pelviureteric junction hydronephrosis is the most frequently diagnosed form of fetal uropathy. Its management and indications for surgery are highly controversial, since the natural history of the disease is unknown. Management is often based on experience with symptomatic conditions in older children which are not necessarily relevant to asymptomatic neonates. The situation is compounded by the fact that assessment of hydronephrosis can be both difficult and misleading.

We present a 6-year study of patients with antenatally suspected PUJ hydronephrosis.

## Patients and Methods

Between 1983 and 1988, 107 consecutive patients who had significant antenatal urological anomalies detected during routine obstetric ultrasound scanning were investigated postnatally. Of these, 45 were found to have PUJ hydronephrosis (66 renal units); 36 patients were male and 9 female. Initial postnatal diagnosis was based on ultrasound (US), intravenous urography (IVU) and $^{99m}$Tc DTPA diuresis renography. The DTPA technique involved a continuous computer acquisition of renographic data over 20 min and delayed analogue images were taken 60 min after micturition. Frusemide was given at 10 min. To exclude vesicoureteric reflux (VUR), most patients (90%) also underwent micturating cystography.

Renal units fell into 2 groups according to the presence or absence of obstruction on both IVU and DTPA renography. Group I had obstruction and group II failed to demonstrate obstruction (non-obstructive hydronephrosis) on initial investigations. All patients had regular follow-up. Repeat imaging was carried out at varying intervals depending on the severity of the initial condition and whether the patient had surgery or not. Improvement or deterioration was based on the change of pattern in morphology (US, IVU) and/or transit time and drainage (IVU, DTPA) during follow-up investigations.

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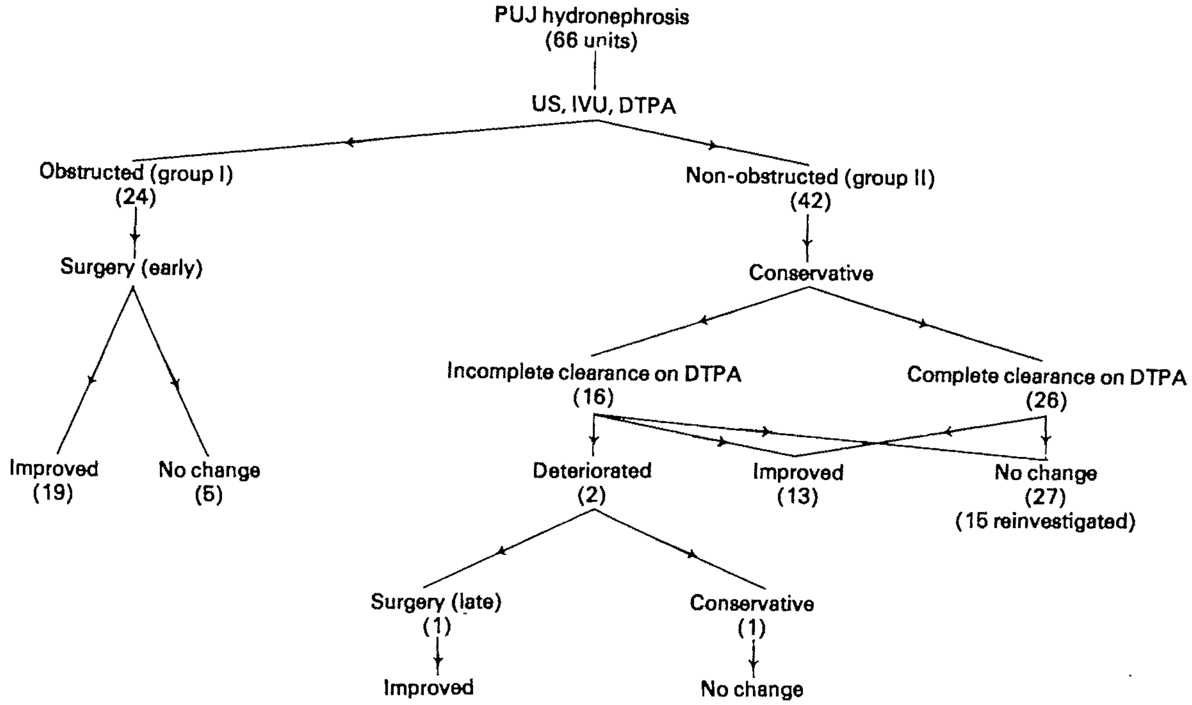

**Fig.** Outcome of antenatally suspected PUJ hydronephrosis.

## Results

### *Group I*

Of 24 renal units (Table, Fig.), antenatal diagnosis was accurate in all but 4, which were reported as cystic kidneys. Postnatal diagnosis was made at a mean age of 4.5 weeks (range 1–26). Prior to treatment, 9 units (38%) had a significant reduction in differential function on renography, ranging from 18 to 40%. Another patient with a solitary affected kidney developed chronic renal failure.

All units were treated by dismembered pyeloplasty (Hynes Anderson). The procedures were done at a mean age of 9 weeks (range 1–39). Postoperative IVU and/or DTPA at 3 months showed improvement in 19 units (79%) and no change in the remaining 5 kidneys. Four of the latter 5 units had significantly reduced pre-operative renal function.

### *Group II*

There were 42 renal units in this group (Table, Fig.). Antenatal diagnosis was accurate in 35 (83%). One unit was reported as cystic and the remaining 6 were found during postnatal investigations for antenatally described contralateral abnormalities.

**Table** Initial Diagnosis

| | *Unilateral hydronephrosis* | *Unilateral hydronephrosis with contralateral pathology* | *Bilateral hydronephrosis** |
|---|---|---|---|
| Group 1 (Obstructed) | 10 | 3<br>Agenesis 1<br>VUR 1<br>Multicystic 1 | 3 |
| Group 2 (Non-obstructed) | 9 | 2<br>VUR 1<br>Multicystic 1 | 13 |

*5 patients had one side obstructed and the other non-obstructed.

Three renal units appeared normal on early postnatal US but were found to be significantly dilated at subsequent investigations. Initial diagnosis of non-obstructive hydronephrosis was established at a mean age of 8 weeks (range 1–52). Diuresis renography showed clearance to be complete in 26 units (62%) and incomplete (equivocal washout) in 16. Reduced differential function was not evident in any unit.

In 2 patients who had incomplete clearance on the initial DTPA scan, 2 renal units (5%) deteriorated during follow-up (prolonged transit time and worsening drainage). In 1 unit, deterioration occurred at the age of 31 months on the fifth DTPA scan and the appearance has since remained static. The other unit developed the appearance of complete obstruction at the age of 7 months on the third DTPA scan and required pyeloplasty. This patient's post-operative scan has shown a definite improvement. Neither of these units suffered infection at any stage.

At a mean age of 8 months (range 1–15), 13 units (31%) showed signs of improvement and 2 of these have returned to normal. These improvements were noticed on US alone in 3 and US with either IVU and/or DTPA in the remaining 10.

Of the remaining 27 units (64%), 15 (56%) have been reinvestigated and at a mean age of 28 months (range 6–53) these have remained static. These investigations comprised US alone in 3 units and US with IVU and/or DTPA in the remaining 12.

## Discussion

In this region, the incidence of apparent PUJ hydronephrosis among patients with an abnormal antenatal renal US scan was 42%, with a male to female ratio of 4 to 1. Accepting the limitations of existing investigation modalities (O'Reilly, 1986; Elder and Ducket, 1988), a significant proportion of the renal units (36%) had obstruction. Whilst only 3 patients (7%) had bilateral obstruction, 21 (47%) had some degree of bilateral hydronephrosis. Since 5 patients had other contralateral upper tract pathology, the overall incidence of bilateral disease was 58% (Table). This may have important implications when deciding which patient may safely be treated conservatively.

It has been suggested that asymptomatic antenatally diagnosed PUJ obstruction can be managed conservatively, since this form of obstruction seems relatively benign and may even resolve spontaneously (Thomas and Gordon, 1989). Others have suggested that kidneys that show good preservation of function on isotope scan can be managed conservatively even if there is evidence of active obstruction, while evidence of impaired differential function <40% is an indication for surgery (Ransley and Manzoni, 1985). Early surgery has been advocated in all cases of PUJ obstruction because it offers an opportunity to preserve renal tissue and because pyeloplasty is a relatively safe procedure even in the neonatal period (Flake *et al.*, 1986; Reinberg and Gonzalez, 1987; Guys *et al.*, 1988; Hanna and Gluck, 1988). Our finding of clinical renal failure in 1 patient and significantly reduced differential renal function on isotope renography in 38% of renal units with obstruction, demonstrates the seriousness of the impact that obstruction may exert on renal tissue. Therefore we do not agree that asymptomatic PUJ obstruction is a benign condition.

Deterioration of PUJ non-obstructive hydronephrosis to obstruction has only rarely been reported (Homsy *et al.*, 1986; Noe and Magill, 1987). In this study, excluding the 3 units which were normal on initial postnatal US and abnormal on subsequent investigations, such deterioration was seen in 2 units (5%). Both of these units had equivocal washout on earlier investigations and only 1 has required surgery so far.

Our results show the outcome of a policy based on the presence of obstruction in PUJ hydronephrosis assessed by US, IVU and diuresis renography. We feel that this approach is logical and safe, since reduced function was observed only in obstructed units. However, the limitations of current investigations must be remembered in the assessment of individual patients. To await the loss of renal function before intervening surgically would seem unwise, but may happen despite close follow-up.

At this early stage of follow-up, non-obstructive hydronephrosis appears to be a relatively benign condition and may safely be managed conservatively; it is essential to continue the long-term follow-up of these patients in order to determine the natural history of the condition.

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# Case Reports

## A Pitfall in the Diagnosis of Supernumerary Kidney

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### Case Report

A 25-year-old hypertensive male patient complained of right loin pain of 1 month's duration. Ten years before he had sustained blunt trauma to the right kidney which was managed conservatively.

Multiple stones were seen in a small hydronephrotic right kidney (Figs 1A and B) and these were confirmed by ultrasound. DMSA renal scan showed decreased uptake in the upper two-thirds.

A small shrunken hydronephrotic right kidney (6 cm long) was removed with an intact capsule. Following this, the drain kept producing urine. Further investigations showed a completely formed kidney with a separate artery. The possibility of supernumerary kidney was then contemplated.

A complete kidney (Fig. 1C) high up in the subhepatic fossa (5 cm long) was removed at a second operation.

### Comment

Supernumerary kidney is an extremely rare renal anomaly (Witten *et al.*, 1977) and prior to 1981, 63 cases had been reported in the English literature (Tada *et al.*, 1981). The anomaly is more frequent on the left side (63.3%) and usually caudal to the ipsilateral kidney (55.2%) (N'Guessan and Stephens, 1983). Stones occurred more often in the ipsilateral kidney; in our case stones were in both.

Pre-operative diagnosis is difficult. The overlap of the 2 kidneys, as in our case, may cause problems in diagnosis and complete removal, especially if 1 kidney is surrounded by dense adhesions.

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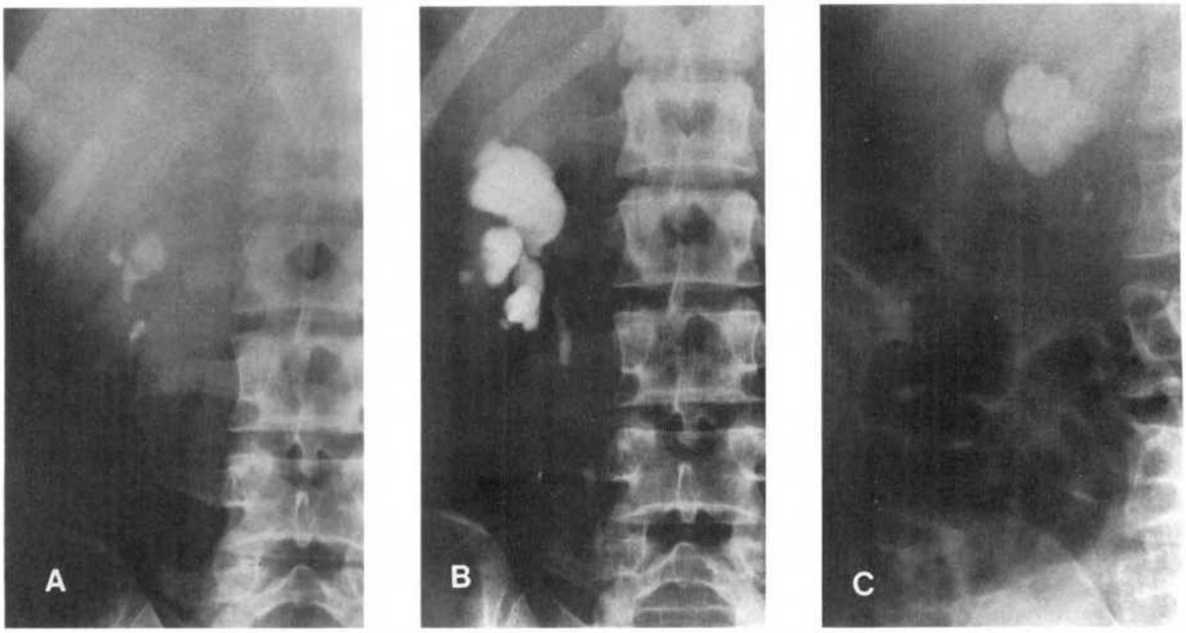

**Fig. 1** (A) Multiple stones, right kidney. (B) Grossly hydroephrotic right kidney. (C) Dilated calices in supernumerary kidney.

# Nephrogenic Adenoma of the Renal Pelvis

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## Case Report

In October 1982 a 36-year-old man underwent radical cystectomy and ileocaecal conduit urinary diversion for a transitional cell bladder tumour (pT4a G3 pNO MO), receiving adjuvant chemotherapy with methotrexate afterwards (1 g/m$^2$/21 days, 19 courses). During 1985 and 1986 he developed multiple infective renal calculi which, in spite of local chemolysis with Renacidin, led to 2 bilateral percutaneous nephrolithotomies. Four months after the first percutaneous procedure a stricture of the left pelviureteric junction (PUJ) was detected and a percutaneous nephrostomy performed (Fig. 1). The patient refused further surgery to correct the PUJ stricture until November 1988, when he underwent another left percutaneous nephrolithotomy and endopyelotomy. During the procedure a small papillary tumour, situated at the PUJ and the anterior pelvic wall, was seen and biopsed. Histology revealed a nephrogenic adenoma of the renal pelvis (Fig. 2).

## Comment

Nephrogenic adenoma is an uncommon lesion of the urothelium, first described by Davis in 1949 and subsequently characterised in detail and named by Friedman and Kuhlenbeck in 1950. It has been encountered along the entire urinary tract, although its most frequent anatomical site is the bladder (72%). Other sites are less frequently affected: ureter 8%, urethra 9%, renal pelvis 11% (McIntire *et al.*, 1987). It is thought to arise as an immature metaplastic response of transitional epithelium to chronic inflammation and is considered benign, although in many instances it appears associated with a bladder carcinoma.

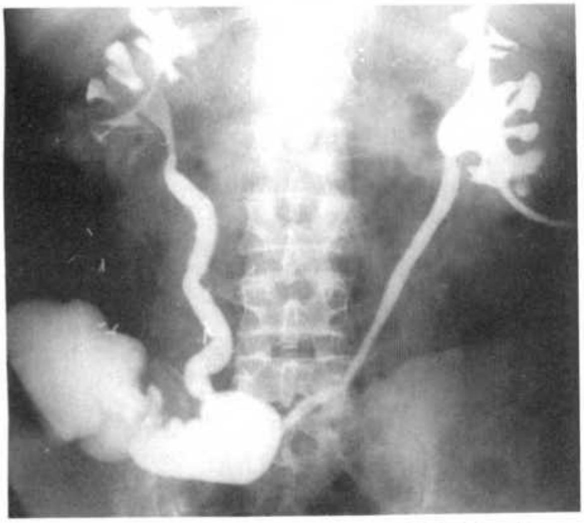

**Fig. 1** Left antegrade pyelogram showing left PUJ stricture, the ileocaecal conduit and reflux to the right urinary system. No filling defect can be seen in the left renal pelvis.

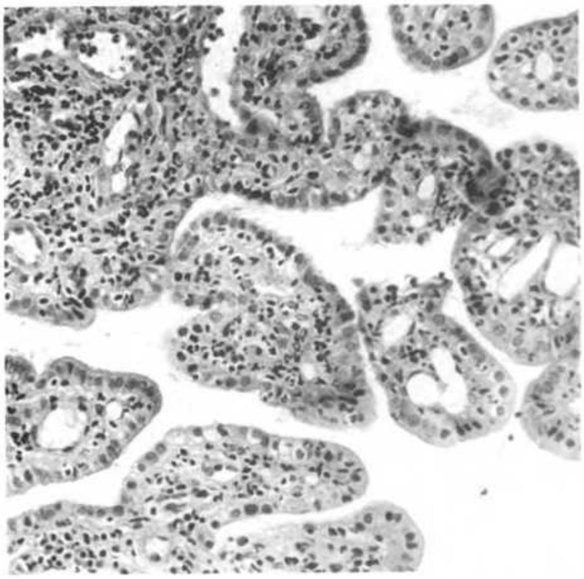

**Fig. 2** Nephrogenic adenoma. Papillary processes covered by a single layer of cuboidal epithelium together with small tubular structures are seen within the lamina propria. (H and E × 25).

Various predisposing factors have been proposed: congenital factors, chronic cystitis, urinary infection, calculi, previous surgery, renal transplant immunosuppression, bladder cancer, intravesical chemotherapy and immunotherapy, malakoplakia and diverticula. In our case several of these factors may have been at work.

The frequent papillary appearance and the microscopic resemblance to clear cell adenocarcinoma of the urinary tract make the histological distinction essential in the diagnosis and treatment.

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# Urinary Obstruction due to Labial Fusion

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## Case Report

The first case of urinary obstruction due to fusion of the labia minora is reported.

Routine antenatal ultrasound scanning at 38 weeks revealed a female fetus with a grossly distended bladder.

After a normal delivery at term, the bladder appeared to empty normally, but 2 post-natal ultrasound scans showed a large bladder with normal upper tracts.

The patient was therefore managed expectantly but at 6 months of age a bladder was, for the first time, palpable suprapubically. No evidence of urinary infection was found.

Cystoscopy was performed to exclude urethral causes of obstruction and complete fusion of the labia minora with no obvious urinary exit was seen. The labia were separated and cytoscopy revealed a moderately trabeculated bladder wall with normal ureteric orifices.

Review 6 weeks post-operatively showed the labia to have remained separated and ultrasound repeated at 6 months revealed a normal diameter bladder.

## Comment

The association between male phimosis and urinary outflow obstruction has been considered (Bartone and King, 1986) and is recognised as a discrete, if unusual, entity.

Labial fusion, the female equivalent of phimosis, is recognised but not as a congenital lesion (Finlay, 1975), unlike our case. Though possibly associated with urinary infections, labial fusion has not been cited as a cause of urinary outflow obstruction (Lyon and Tanagho, 1965).

Our patient demonstrated bladder distension (at increased voiding pressures manifested by trabeculation) associated with labial fusion which was complete on macroscopic inspection.

The resolution of the bladder distension following the division of such a substantial impedance to flow is unlikely to have occurred by coincidence.

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# Vulvar and Vaginal Implantation of Transitional Cell Carcinoma of the Urinary Tract

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## Case Report

In 1978 a frail 73-year-old lady first presented with a Stage T1, Grade 2 papillary transitional cell carcinoma of the bladder, which was treated by endoscopic resection. No known aetiological factors were identified. During the following 10 years she underwent several endoscopic procedures for recurrent multifocal Ta–1, G1–2 transitional cell carcinoma of the bladder. The disease eventually also involved the upper urinary tracts. In 1983 a partial resection of the right distal ureter and ureteric reimplantation with bladder hitch procedure was necessary for recurrent tumour (Ta, G1). Intravesical instillations with thiotepa and ethoglucid (Epodyl) were ineffective.

In December 1984 a tumour recurrence at the external urethral meatus and second tumour about 1 cm from it on the vulva were detected. Both were resected. Thereafter, monthly bladder instillations with mitomycin resulted in a recurrence-free period of 2 years until urine cytology again became positive and a recurrence near the external urethral meatus reappeared. Simultaneously, a lesion on the dorsal vaginal wall was found. Histology of the excised specimens confirmed both to be non-invasive Grade 1 transitional cell carcinoma. Several recurrences in the bladder and vagina were treated locally during the following months. In July 1987 a reddish painless lump, 0.6 cm in diameter, was excised from the left lateral vaginal wall (Fig. 1). Microscopic examination confirmed a Grade 2 papillary transitional cell carcinoma surrounded by normal squamous vaginal epithelium and with no invasion (Fig. 2).

In September 1987 a right nephroureterectomy was necessary for multiple recurrences in the remaining right

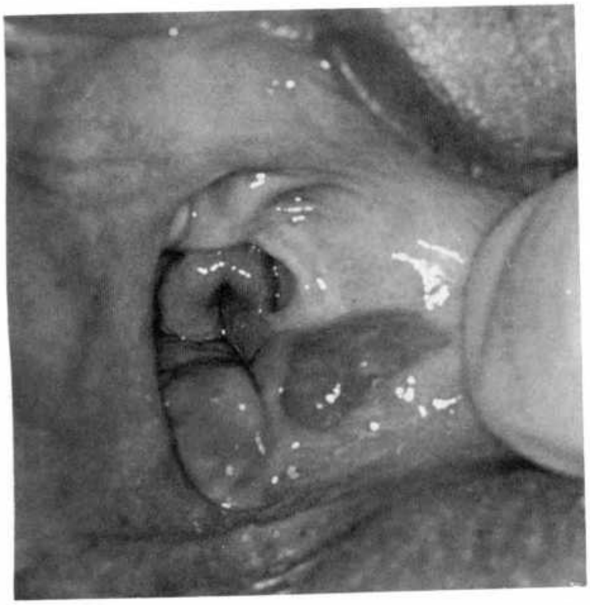

**Fig. 1** The mass on the left lateral vaginal wall, close to the introitus, prior to excision.

ureter, resulting in non-function of the kidney. One month later, at the age of 82, the patient died, at home, of progressive renal insufficiency and diabetes mellitus, but without clinical evidence of transitional cell carcinoma of the bladder elsewhere.

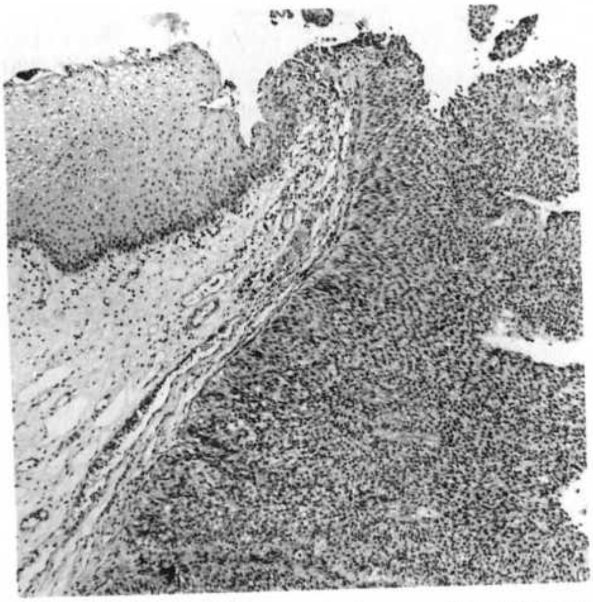

**Fig. 2** Histopathology of the excised tumour of the left lateral vaginal wall. Note the presence of normal vaginal squamous epithelium next to papillary transitional cell carcinoma. There is no invasion of the adjacent tissues. (H and E × 12.)

## Comment

In this case, lymphatic or vascular spread of tumour cells to the vulvar or vaginal epithelium is difficult to postulate, since infiltration beyond the lamina propria was not seen in any of the biopsies of urinary tract tumours, nor were any signs of vascular or lymphatic involvement around the vaginal or vulvar lesions (Dehner, 1973).

Implantation of shedded tumour cells in tissues "downstream" during micturition or resection seems the only plausible alternative. Whether tumour cell implantation can be considered a cause of tumour spread to adjacent normal non-urothelial epithelium remains to be determined. In view of our findings, the possibility of this pathway needs perhaps to be borne in mind (Boyd and Burnand, 1974; Weldon and Soloway, 1975; Soloway, 1983).

To our knowledge, superficial vulvar or vaginal implantation of a transitional cell tumour of the urinary tract has not previously been reported.

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# Transitional Cell Carcinoma Arising in a Urachal Cyst

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By far the most common urachal malignancy is adenocarcinoma. We report a case of transitional cell carcinoma developing within a urachal cyst.

A 65-year-old woman presented as an emergency with a painful umbilical mass. She had no urinary symptoms. At operation a 4 × 5 cm loculated cyst was found lying within a defect in the midline of the rectus sheath, caudal to the umbilicus; there was no communication with the peritoneal cavity. The cyst was excised intact and the defect in the sheath was repaired.

Histologically, the cyst was lined with transitional epithelium (Fig. 1), part of which had undergone malignant change; there was both local and lymphatic spread. Subsequent urine microscopy, cytology, IVU, abdominal ultrasonography, cystoscopy and EUA were all normal. A planned abdominal and pelvic CT scan was refused by the patient, but subsequently performed, 6 months postoperatively, after routine clinical examination revealed a new umbilical mass. The scan (Fig. 2) demonstrated tumour spreading diffusely beneath the abdominal wall and transitional cell carcinoma was confirmed histologically on Tru-cut biopsy.

The patient remains asymptomatic 12 months postoperatively and under review with no further surgery being contemplated.

## Comment

Carcinoma of the urachus is rare, accounting for less than 1 in 1400 tumours associated with the bladder; 90% of cases arise from the intra- or juxtavesical end of the urachus and are predominantly mucus-producing adenocarcinoma (Beck *et al.*, 1970). The remainder are of supravesical origin; these are mainly undifferentiated or transitional cell tumours (Hayman, 1984). Our case belongs to the latter group.

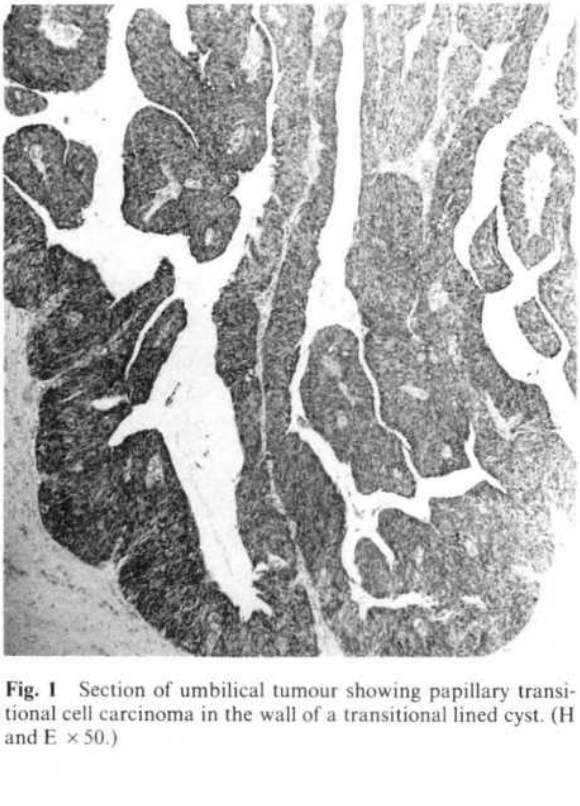

Fig. 1 Section of umbilical tumour showing papillary transitional cell carcinoma in the wall of a transitional lined cyst. (H and E × 50.)

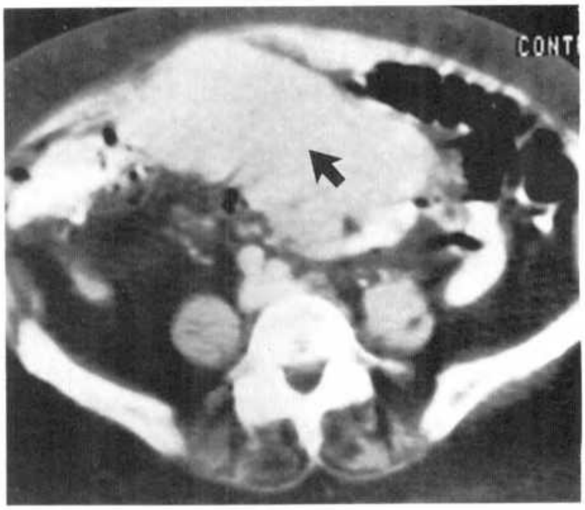

**Fig. 2** CT scan at the level of iliac crest, showing large mass of soft tissue density (arrowed).

To our knowledge, only 3 cases of carcinoma arising in a urachal cyst have been reported in the literature to date; 2 of these were adenocarcinoma (Whitehead and Tessler, 1971), the other squamous cell (Beck *et al.*, 1970).

The overall prognosis for a urachal carcinoma is poor; Whitehead and Tessler (1971) quoted a 41% 1-year and 91% 5-year mortality rate in a series of 133 cases.

## Acknowledgement

We thank Dr D. F. R. Griffiths, Senior Lecturer in Pathology, for the photomicrograph (Fig. 1).

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Requests for reprints to: P. P. Irwin, Department of Urology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

# Non-palpable Testes in an 18-year-old Patient with Klinefelter's Syndrome: Is Surgery Indicated?

M. S. BORNMAN, E. L. KOK and D. J. DU PLESSIS,
*Spermatology Laboratory, Department of Urology,*
*University of Pretoria, Pretoria, South Africa*

An 18-year-old male was referred with an empty scrotum. On examination he was extremely tall (220 cm). No testes were palpable either in the scrotum, inguinal region or elsewhere. Laboratory tests showed azoospermia and markedly elevated LH and FSH, with lowered serum testosterone. On CT scan no testes or abnormal masses were seen. The peripheral chromosomal karyotype was 47,XXY (Klinefelter's syndrome). On exploration small inguinal testes were found bilaterally, but orchiolysis and orchiopexy were impossible. Histology showed Sertoli cells, many hyalinised tubules and Leydig cell hyperplasia.

## Comment

In boys with cryptorchidism the incidence of both Klinefelter's syndrome and testicular tumours is higher. Patients with Klinefelter's syndrome have a greater incidence of breast cancer and leukemia than the general population (Sogge *et al.*, 1979). These patients may also develop mediastinal extragonadal germ cell tumours more frequently (Carroll *et al.*, 1988); they have, however, a low incidence of seminomas but a higher incidence of choriocarcinomas (Carroll *et al.*, 1988). Other testicular tumours include Leydig cell carcinoma (Sogge *et al.*, 1979; Carroll *et al.*, 1988; Dexeus *et al.*, 1988), teratoma and embryonal carcinoma (Dexeus *et al.*, 1988).

Although the hypergonadotrophic azoospermia might point towards the absence of germinal epithelium, the extent and composition of the remaining seminiferous tissue would not have been clear without histology. Therefore, it would seem that exploration and orchiectomy might be indicated in cases like these.

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# Stuttering Priapism in Sickle Cell Disease

A. A. ADOGU, *Department of Internal Medicine, Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria*

## Case Report

A 15-year-old Nigerian boy presented with a 2-day history of sudden, painful penile erection with intermittent detumescence. He had been diagnosed as suffering from sickle cell anaemia in infancy, with genotype Hb SS. There was no history of previous priapism, recent drug ingestion or neuro-psychiatric disturbance. Examination revealed a pale, dehydrated, anicteric adolescent with a full non-pulsatile penile erection and engorged superficial penile veins. The urethral meatus, scrotum and rectum were normal.

Investigations showed a Hb of 7.0 g/dl, WBC count $13.3 \times 10^9$/l (neutrophils 60%, lymphocytes 35%, monocytes 5%, basophils 0%, eosinophils 0%); platelets 240,000/mm$^3$; blood smear showed no parasitaemia, but numerous sickled cells and occasional target cells. Blood biochemistry was normal.

Treatment was started with intravenous 5% dextrose-saline, 500 ml every 3 h and intramuscular pentazocine 12.5 mg *stat.* with atropine 0.3 mg by slow intravenous infusion every 6 h. Oral prophylactic chloroquine and vitamin supplementation were commenced. Sustained detumescence was noted on the second post-admission day; recovery was sustained and complete.

## Comment

Priapism refers to a painful, persistent, phylogenetically purposeless penile erection, being related neither to sexual arousal nor to the facilitation of sexual intercourse. It is associated with blood dyscrasias, carcinomatoses, neuro-psychiatric disorders, haemodialysis, hypotension, androgen excess, idiosyncratic drug reactions, etc (Narayana *et al.*, 1977). The commonest cause of priapism in Nigeria is sickle cell anaemia, which affects 1.5% of her paediatric population; priapism occurring during vascular "thrombotic crises" in these patients is usually sustained and results in impotence (Ihekwaba, 1980).

Priapism in sickle cell disease may result from vascular stasis following normal physiological nocturnal erection, dehydration, relative metabolic acidosis associated with sleep, all inducing erythrocyte sickling within the corpora cavernosa. Recent reports indicate that priapism may be secondary to prazosin therapy (an $\alpha 2$-adrenergic neurone blocker), dysautonomia, spinal cord injury, mental disorders and early rabies (Udwadia *et al.*, 1988). Indeed, a "stuttering" spasmodic disease suggests a neurogenic alteration in vascular tone due to fluctuating autonomic imbalance rather than the alternative hypothesis of cycles of obstruction/recanalisation, which is in keeping with the good prognosis of this sub-type, with response to parasympatholytic therapy.

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Requests for reprints to: A. A. Adogu, Department of Clinical Biochemistry, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QR.

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## Carcinosarcoma of the Bladder

A. GIANNOPOULOS, G. ALIVIZATOS, V. KYRIAKOU, D. MITROPOULOS and M. A. DIMOPOULOS, *Department of Urology, Laiko Hospital, Athens, Greece*

Carcinosarcoma is a tumour consisting of malignant epithelial and mesenchymal components; it is a rare lesion and approximately 50 cases have been reported, usually as single case reports (Sommer *et al.*, 1988).

### Case Report

A 74-year-old woman presented in January 1988 with a 6-month history of gross haematuria and dysuria. Physical examination was unremarkable and an intravenous urogram demonstrated incomplete filling of the right side of the bladder. Chest X-ray was normal and laboratory tests revealed slight anaemia. Cystoscopy was performed and a 5 × 5 cm sessile mass was found. Biopsies revealed a malignant tumour consisting mainly of grade II

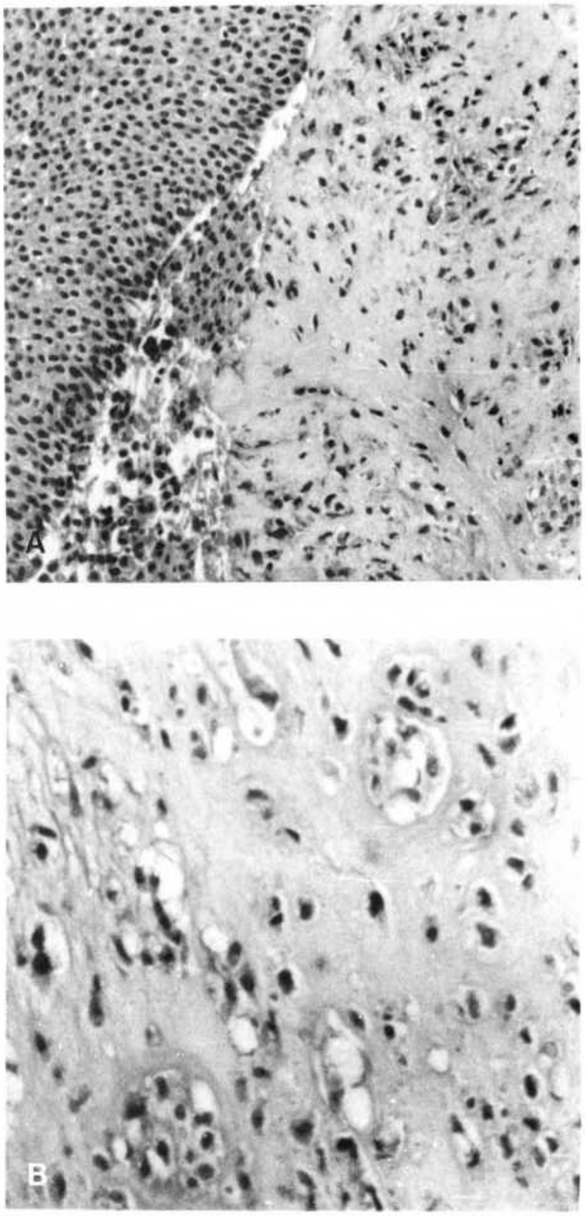

**Fig. 1.** (A) Mixed histological pattern with elements of transitional cell carcinoma and chondrosarcoma. (H and E × 30.) **(B)** Chondrosarcomatous elements at higher magnification. (H and E × 200.)

transitional cell carcinoma but with foci of chondrosarcoma elements.

A computed tomography scan of the abdomen and pelvis showed no evidence of distant metastatic disease.

Radical cystectomy was recommended but the patient's relatives refused such therapy and so partial cystectomy was carried out. The surgical specimen consisted of a 6 × 6 × 5.5 cm mass at the right bladder wall. The chondrosarcomatous elements are shown in the Figure. Immunohistochemical staining for cytokeratin and epithelial membrane antigen was negative.

The patient was treated with chemotherapy consisting of methotrexate, cisplatin and vinblastine. She was in good health 12 months post-operatively.

## Comment

It is important to distinguish carcinosarcoma of the bladder from carcinomas with spindle areas. In order to exclude spindle cell carcinoma the sarcomatous element of the tumour must be identified as rhabdo-, osteo- or chondro-sarcoma (Mostofi *et al.*, 1988) and immunohistochemical staining for cytokeratin and epithelial membrane antigen should be carried out on the sections. If these are negative, any spindle cell tumour may reasonably be considered sarcomatous. Because of the limited number of similar cases reported, the natural history of these tumours and the best methods of treatment are uncertain. It seems that radical cystectomy with or without pre-operative radiation represents the treatment of choice (Young, 1987).

Carcinosarcoma of the bladder has a poor prognosis and the 5-year survival rate is only 20% (Sen *et al.*, 1985).

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Requests for reprints to: A. Giannopoulos, Department of Urology, Laiko Hospital, 115 27 Athens, Greece.

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# Wegener's Granulomatosis Presenting as Prostatitis

G. E. MURTY and P. H. POWELL, *E.N.T. Department and Department of Urology, Freeman Hospital, Newcastle upon Tyne*

## Case Report

A 37-year-old man presented with a 2-month history of urinary frequency and intermittent dysuria. Examination was normal. Urine analysis revealed microscopic haematuria and a sterile pyuria. An IVU was normal. Urethroscopy showed a mild anterior urethritis with diffuse enlargement of the prostate and contact bleeding. Transrectal biopsy of the prostate was undertaken. Histology showed a necrotising granulomatous prostatitis (Fig.) with no evidence of malignancy or acid-fast bacilli.

The patient improved symptomatically following cystoscopy but presented 1 month later with chest pain, haemoptysis and cough. Chest X-ray revealed a cavitating lesion which on biopsy proved to be Wegener's granulomatosis. This was confirmed by an elevated anti-neutrophil cytoplasmic antibody titre. He is presently in remission following a course of combined cyclophosphamide and prednisolone.

## Comment

Wegener's granulomatosis is characterised by necrotising granulomata with vasculitis, commonly

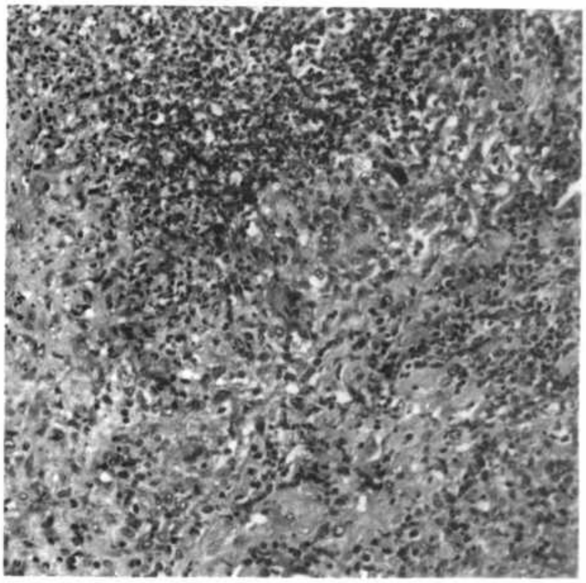

**Fig.** Prostatic biopsy showing necrotising endarteritis and multinucleate giant cells.

involving the upper and lower respiratory tracts and the kidneys. The pathognomonic lesion is rarely present in all affected sites and the diagnosis is made from a combination of clinical and histological findings (Fauci *et al.*, 1983). More recently the anti-neutrophil cytoplasmic antibody (ANCA) test has been developed as an aid to diagnosis (Van der Woude *et al.*, 1985).

Prostatic involvement can present as urinary obstruction, infection or haematuria. It is a late feature and occurs in 2.3% of cases (Stillwell *et al.*, 1987). Only 3 cases have previously been reported where prostatic involvement alone was the first clinical evidence of Wegener's granulomatosis. The treatment of choice is combined immunosuppressive therapy. Cytotoxics, commonly cyclophosphamide or azathioprine, are given with corticosteroids until remission is achieved. Long-term survival is now possible.

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Requests for reprints to: G. E. Murty, E.N.T. Department, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN.

British Journal of Urology (1991), 67, 109

# Point of Technique

## Removal of Ureteric Stents with a Flexible Cystoscope

J. W. H. EVANS and D. J. RALPH, *Department of Urology, Middlesex Hospital, London*

Soft ureteric stents are usually removed under topical anaesthesia with the flexible cystoscope to avoid further anaesthesia. Various instruments have been advocated for grasping the stent, but all have some disadvantages.

The fibrescopic biopsy forceps are unsuitable because of the tiny jaws which usually slip off or damage the stent. A loop of nylon glued into a 5 F ureteric catheter (Blandy and Fowler, 1986; Fowler, 1987) or a 4 F Dormia basket (Upsdell, 1988) have been suggested. Both of these methods have the disadvantage of requiring manipulation of the loop or basket over the free end of the stent. This can be very difficult and time-consuming in a busy procedures clinic.

A simpler and faster method which requires no such manipulation is to use the 3-pronged grasping forceps. The flexible cystoscope is introduced with the forceps positioned so that the tip lies just at the end of the instrument channel. The stent is easily visualised immediately on entering the bladder (Fig. A). The grasping forceps are opened so that any visible part of the stent lies between the prongs (Fig. B). The forceps are closed and the flexible cystoscope, 3-pronged grasping forceps and stent are withdrawn slowly and gently (Fig. C).

This is the method of stent removal currently employed at the Middlesex Hospital. No complex manipulations are required and it is recommended as the method of choice for removing soft double-J ureteric stents.

### Acknowledgement

We thank the Department of Medical Illustration at the Middlesex Hospital for their help.

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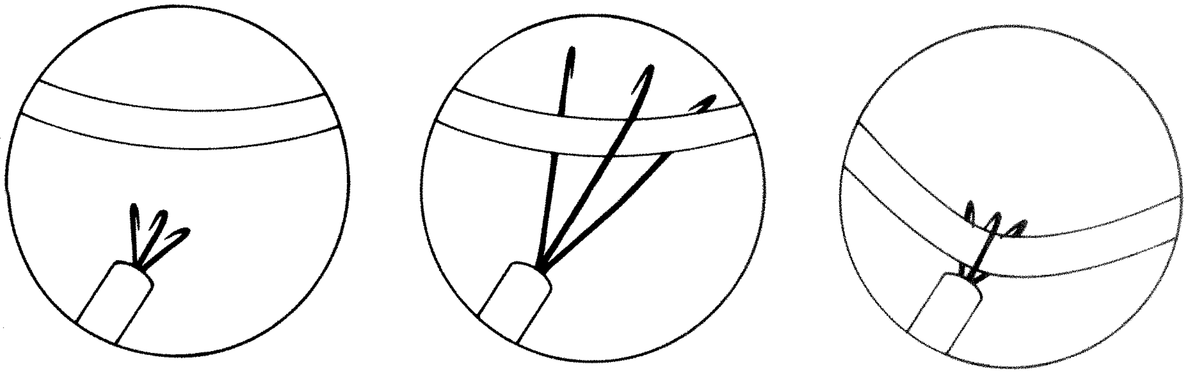
Requests for reprints to: J. H. W. Evans, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.



**Figure**

*British Journal of Urology* (1991), **67**, 110

# Notices

## Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

## Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

## Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

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# Diary

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|---|---|
| ebruary 3–6 | International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India. |
| ebruary 7–8 | Uro-Radiology '91. For further details of this course please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| ebruary 23–<br>arch 2 | Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ. |
| arch 11–15 | Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| arch 16–17 | International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| pril 8–28 | Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| pril 12–13 | Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France. |
| ril 14–19 | Forty-fourth Annual Scientific Meeting of the Urological Society of Australasia, Sheraton Mirage Hotel, Gold Coast, Queensland, Australia. Contact: G. Holmes, President, Brisbane Urology Clinic, 11th Floor, 149 Wickham Terrace, Brisbane, QLD 4000. |
| ay 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi-Belgium. |
| e 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| e 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |

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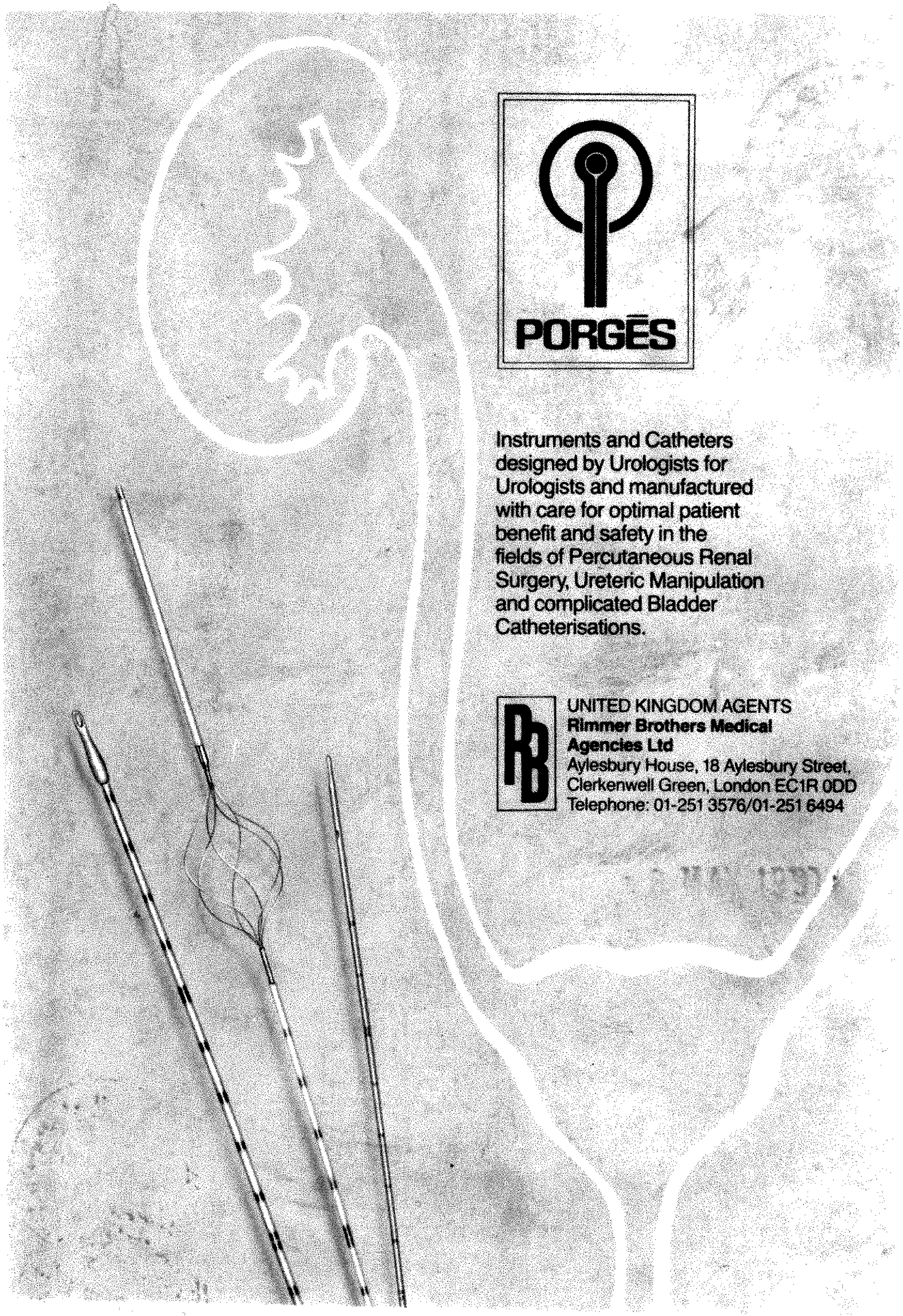
| June 12–15 | Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9. |
| June 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
| July 2–3 | Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |
| 1992 | |
| January 10 | Final date for submission of abstracts for the 1992 BAUS Annual Meeting. |
| May 10–14 | American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC. |
| June 21–26 | BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office. |
| June 22–25 | Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| August 24–27 | Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. |
| 1993 | |
| May 16–20 | American Urological Association, San Antonio Convention Centre, San Antonio, Texas. |



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